HETEROBICYCLIC METALLOPROTEASE INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority from U.S. Provisional Application No. 60/734,991, filed November 9, 2005; U.S. Provisional Application No. 60/706,465, filed August 8, 2005; and U.S. Provisional Application No. 60/683,470 filed May 20, 2005, the contents of each of which are hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates generally to amide containing heterobicyclic metalloprotease inhibiting compounds, and more particularly to heterobicyclic MMP-13 inhibiting compounds.

BACKGROUND OF THE INVENTION

[0003] Matrix metalloproteinases (MMPs) and aggrecanases (ADAMTS = a disintegrin and metalloproteinase with thrombospondin motif) are a family of structurally related zinc-containing enzymes that have been reported to mediate the breakdown of connective tissue in normal physiological processes such as embryonic development, reproduction, and tissue remodelling. Over-expression of MMPs and aggrecanases or an imbalance between extracellular matrix synthesis and degradation has been suggested as factors in inflammatory, malignant and degenerative disease processes. MMPs and aggrecanases are, therefore, targets for therapeutic inhibitors in several inflammatory, malignant and degenerative diseases such as rheumatoid arthritis, osteoarthritis, osteoporosis, periodontitis, multiple sclerosis, gingivitis, corneal epidermal and gastric ulceration, atherosclerosis, neointimal proliferation (which leads to restenosis and ischemic heart failure) and tumor metastasis.

[0004] The ADAMTSs are a group of proteases that are encoded in 19 ADAMTS genes in humans. The ADAMTSs are extracellular, multidomain enzymes whose functions include collagen processing, cleavage of the matrix proteoglycans, inhibition of angiogenesis and blood coagulation homoeostasis (*Biochem. J.* **2005**, *386*, 15-27; *Arthritis Res. Ther.*

2005, *7*, 160-169; *Curr. Med. Chem. Anti-Inflammatory Anti-Allergy Agents* **2005**, *4*, 251-264).

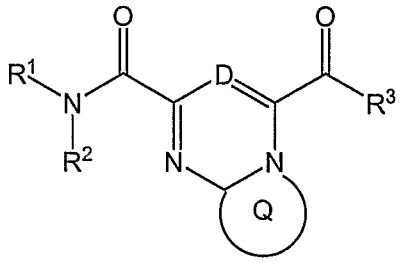
[0005] The mammalian MMP family has been reported to include at least 20 enzymes, (*Chem. Rev.* **1999**, *99*, 2735-2776). Collagenase-3 (MMP-13) is among three collagenases that have been identified. Based on identification of domain structures for individual members of the MMP family, it has been determined that the catalytic domain of the MMPs contains two zinc atoms; one of these zinc atoms performs a catalytic function and is coordinated with three histidines contained within the conserved amino acid sequence of the catalytic domain. MMP-13 is over-expressed in rheumatoid arthritis, osteoarthritis, abdominal aortic aneurysm, breast carcinoma, squamous cell carcinomas of the head and neck, and vulvar squamous cell carcinoma. The principal substrates of MMP-13 are fibrillar collagens (types I, II, III) and gelatins, proteoglycans, cytokines and other components of ECM (extracellular matrix).

[0006] The activation of the MMPs involves the removal of a propeptide, which features an unpaired cysteine residue complexes the catalytic zinc (II) ion. X-ray crystal structures of the complex between MMP-3 catalytic domain and TIMP-1 and MMP-14 catalytic domain and TIMP-2 also reveal ligation of the catalytic zinc (II) ion by the thiol of a cysteine residue. The difficulty in developing effective MMP inhibiting compounds comprises several factors, including choice of selective versus broad-spectrum MMP inhibitors and rendering such compounds bioavailable via an oral route of administration.

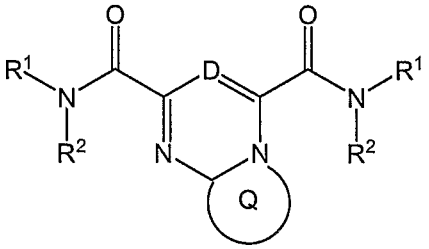
SUMMARY OF THE INVENTION

[0007] The present invention relates to a new class of heterobicyclic amide containing pharmaceutical agents which inhibits metalloproteases. In particular, the present invention provides a new class of metalloprotease inhibiting compounds that exhibit potent MMP-13 inhibiting activity and/or activity towards MMP-3, MMP-8, MMP-12, ADAMTS-4, and ADAMTS-5.

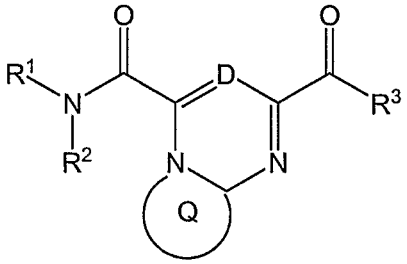
[0008] The present invention provides several new classes of amide containing heterobicyclic metalloprotease compounds, of which some are represented by the following general formulas:



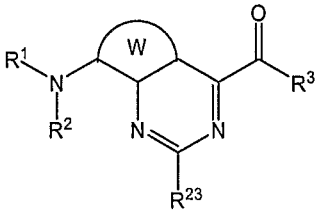
Formula (I)



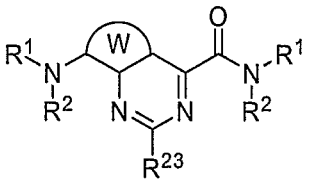
Formula (II)



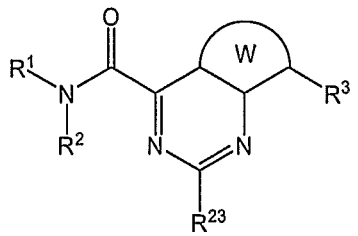
Formula (III)



Formula (IV)



Formula (V)



Formula (VI)

wherein all variables in the preceding Formulas (I) to (VI) are as defined hereinbelow.

[0009] The heterobicyclic metalloprotease inhibiting compounds of the present invention may be used in the treatment of metalloprotease mediated diseases, such as rheumatoid arthritis, osteoarthritis, abdominal aortic aneurysm, cancer, inflammation, atherosclerosis, multiple sclerosis, chronic obstructive pulmonary disease, ocular diseases, neurological diseases, psychiatric diseases, thrombosis, bacterial infection, Parkinson's disease, fatigue, tremor, diabetic retinopathy, vascular diseases of the retina, aging, dementia, cardiomyopathy, renal tubular impairment, diabetes, psychosis, dyskinesia, pigmentary abnormalities, deafness, inflammatory and fibrotic syndromes, intestinal bowel syndrome, allergies, Alzheimer's disease, arterial plaque formation, periodontal, viral infection, stroke, cardiovascular disease, reperfusion injury, trauma, chemical exposure or oxidative damage to tissues, wound healing, hemorroid, skin beautifying, pain, inflammatory pain, bone pain and joint pain.

[0010] In particular, the heterobicyclic metalloprotease inhibiting compounds of the present invention may be used in the treatment of MMP-13 mediated osteoarthritis and may be used for other MMP-13 mediated symptoms, inflammatory, malignant and degenerative diseases characterized by excessive extracellular matrix degradation and/or remodelling, such as cancer, and chronic inflammatory diseases such as arthritis, rheumatoid arthritis, osteoarthritis atherosclerosis, abdominal aortic aneurysm, inflammation, multiple sclerosis, and chronic obstructive pulmonary disease, and pain, such as inflammatory pain, bone pain and joint pain.

[0011] The present invention also provides heterobicyclic metalloprotease inhibiting compounds that are useful as active ingredients in pharmaceutical compositions for treatment or prevention of metalloprotease – especially MMP-13 – mediated diseases. The present invention also contemplates use of such compounds in pharmaceutical compositions for oral

or parenteral administration, comprising one or more of the heterobicyclic metalloprotease inhibiting compounds disclosed herein.

[0012] The present invention further provides methods of inhibiting metalloproteases, by administering formulations, including, but not limited to, oral, rectal, topical, intravenous, parenteral (including, but not limited to, intramuscular, intravenous), ocular (ophthalmic), transdermal, inhalative (including, but not limited to, pulmonary, aerosol inhalation), nasal, sublingual, subcutaneous or intraarticular formulations, comprising the heterobicyclic metalloprotease inhibiting compounds by standard methods known in medical practice, for the treatment of diseases or symptoms arising from or associated with metalloprotease, especially MMP-13, including prophylactic and therapeutic treatment. Although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. The compounds from this invention are conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

[0013] The heterobicyclic metalloprotease inhibiting compounds of the present invention may be used in combination with a disease modifying antirheumatic drug, a nonsteroidal anti-inflammatory drug, a COX-2 selective inhibitor, a COX-1 inhibitor, an immunosuppressive, a steroid, a biological response modifier or other anti-inflammatory agents or therapeutics useful for the treatment of chemokines mediated diseases.

DETAILED DESCRIPTION OF THE INVENTION

[0014] The terms "alkyl" or "alk", as used herein alone or as part of another group, denote optionally substituted, straight and branched chain saturated hydrocarbon groups, preferably having 1 to 10 carbons in the normal chain, most preferably lower alkyl groups. Exemplary unsubstituted such groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl and the like. Exemplary substituents may include, but are not limited to, one or more of the following groups: halo, alkoxy, alkylthio, alkenyl, alkynyl, aryl (e.g., to form a benzyl group), cycloalkyl, cycloalkenyl, hydroxy or protected hydroxy, carboxyl (--COOH), alkyloxycarbonyl, alkylcarbonyloxy, alkylcarbonyl, carbamoyl (NH_2--CO--), substituted carbamoyl ((R^{10})(R^{11})N--CO-- wherein R^{10} or R^{11} are as

defined below, except that at least one of R^{10} or R^{11} is not hydrogen), amino, heterocyclo, mono- or dialkylamino, or thiol (--SH).

[0015] The terms "lower alk" or "lower alkyl" as used herein, denote such optionally substituted groups as described above for alkyl having 1 to 4 carbon atoms in the normal chain.

[0016] The term "alkoxy" denotes an alkyl group as described above bonded through an oxygen linkage (--O--).

[0017] The term "alkenyl", as used herein alone or as part of another group, denotes optionally substituted, straight and branched chain hydrocarbon groups containing at least one carbon to carbon double bond in the chain, and preferably having 2 to 10 carbons in the normal chain. Exemplary unsubstituted such groups include ethenyl, propenyl, isobutenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, and the like. Exemplary substituents may include, but are not limited to, one or more of the following groups: halo, alkoxy, alkylthio, alkyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, hydroxy or protected hydroxy, carboxyl (--COOH), alkyloxycarbonyl, alkylcarbonyloxy, alkylcarbonyl, carbamoyl (NH_2 --CO--), substituted carbamoyl ((R^{10})(R^{11})N--CO-- wherein R^{10} or R^{11} are as defined below, except that at least one of R^{10} or R^{11} is not hydrogen), amino, heterocyclo, mono- or dialkylamino, or thiol (--SH).

[0018] The term "alkynyl", as used herein alone or as part of another group, denotes optionally substituted, straight and branched chain hydrocarbon groups containing at least one carbon to carbon triple bond in the chain, and preferably having 2 to 10 carbons in the normal chain. Exemplary unsubstituted such groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, and the like. Exemplary substituents may include, but are not limited to, one or more of the following groups: halo, alkoxy, alkylthio, alkyl, alkenyl, aryl, cycloalkyl, cycloalkenyl, hydroxy or protected hydroxy, carboxyl (--COOH), alkyloxycarbonyl, alkylcarbonyloxy, alkylcarbonyl, carbamoyl (NH_2--CO--), substituted carbamoyl ((R^{10})(R^{11})N--CO-- wherein R^{10} or R^{11} are as defined below, except that at least one of R^{10} or R^{11} is not hydrogen), amino, heterocyclo, mono- or dialkylamino, or thiol (--SH).

[0019] The term "cycloalkyl", as used herein alone or as part of another group, denotes optionally substituted, saturated cyclic hydrocarbon ring systems, containing one ring with 3 to 9 carbons. Exemplary unsubstituted such groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, and cyclododecyl. Exemplary substituents include, but are not limited to, one or more alkyl groups as described above, or one or more groups described above as alkyl substituents.

[0020] The term "bicycloalkyl", as used herein alone or as part of another group, denotes optionally substituted, saturated cyclic bridged hydrocarbon ring systems, desirably containing 2 or 3 rings and 3 to 9 carbons per ring. Exemplary unsubstituted such groups include, but are not limited to, adamantyl, bicyclo[2.2.2]octane, bicyclo[2.2.1]heptane and cubane. Exemplary substituents include, but are not limited to, one or more alkyl groups as described above, or one or more groups described above as alkyl substituents.

[0021] The term "spiroalkyl", as used herein alone or as part of another group, denotes optionally substituted, saturated hydrocarbon ring systems, wherein two rings are bridged via one carbon atom and 3 to 9 carbons per ring. Exemplary unsubstituted such groups include, but are not limited to, spiro[3.5]nonane, spiro[4.5]decane or spiro[2.5]octane. Exemplary substituents include, but are not limited to, one or more alkyl groups as described above, or one or more groups described above as alkyl substituents.

[0022] The term "spiroheteroalkyl", as used herein alone or as part of another group, denotes optionally substituted, saturated hydrocarbon ring systems, wherein two rings are bridged via one carbon atom and 3 to 9 carbons per ring. At least one carbon atom is replaced by a heteroatom independently selected from N, O and S. The nitrogen and sulfur heteroatoms may optionally be oxidized. Exemplary unsubstituted such groups include, but are not limited to, 1,3-diaza-spiro[4.5]decane-2,4-dione. Exemplary substituents include, but are not limited to, one or more alkyl groups as described above, or one or more groups described above as alkyl substituents.

[0023] The terms "ar" or "aryl", as used herein alone or as part of another group, denote optionally substituted, homocyclic aromatic groups, preferably containing 1 or 2 rings and 6 to 12 ring carbons. Exemplary unsubstituted such groups include, but are not limited to, phenyl, biphenyl, and naphthyl. Exemplary substituents include, but are not limited to,

one or more nitro groups, alkyl groups as described above or groups described above as alkyl substituents.

[0024] The term "heterocycle" or "heterocyclic system" denotes a heterocyclyl, heterocyclenyl, or heteroaryl group as described herein, which contains carbon atoms and from 1 to 4 heteroatoms independently selected from N, O and S and including any bicyclic or tricyclic group in which any of the above-defined heterocyclic rings is fused to one or more heterocycle, aryl or cycloalkyl groups. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom.

[0025] Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolinyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4a*H*-carbazolyl, b-carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinylperimidinyl, oxindolyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl.

[0026] Further examples of heterocycles include, but not are not limited to, "heterobicycloalkyl" groups such as 7-oxa-bicyclo[2.2.1]heptane, 7-aza-bicyclo[2.2.1]heptane, and 1-aza-bicyclo[2.2.2]octane.

[0027] "Heterocyclenyl" denotes a non-aromatic monocyclic or multicyclic hydrocarbon ring system of about 3 to about 10 atoms, desirably about 4 to about 8 atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur atoms, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. Ring sizes of rings of the ring system may include 5 to 6 ring atoms. The designation of the aza, oxa or thia as a prefix before heterocyclenyl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The heterocyclenyl may be optionally substituted by one or more substituents as defined herein. The nitrogen or sulphur atom of the heterocyclenyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. "Heterocyclenyl" as used herein includes by way of example and not limitation those described in Paquette, Leo A. ; "Principles of Modern Heterocyclic Chemistry" (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and "J. Am. Chem. Soc. ", 82:5566 (1960), the contents all of which are incorporated by reference herein. Exemplary monocyclic azaheterocyclenyl groups include, but are not limited to, 1,2,3,4-tetrahydrohydropyridine, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridine, 1,4,5,6-tetrahydropyrimidine, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, and the like. Exemplary oxaheterocyclenyl groups include, but are not limited to, 3,4-dihydro-2*H*-pyran, dihydrofuranyl, and fluorodihydrofuranyl. An exemplary multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl.

[0028] "Heterocyclyl," or "heterocycloalkyl," denotes a non-aromatic saturated monocyclic or multicyclic ring system of about 3 to about 10 carbon atoms, desirably 4 to 8 carbon atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur. Ring sizes of rings of the ring system may include 5 to 6 ring atoms. The designation of the aza, oxa or thia as a prefix before heterocyclyl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The heterocyclyl may be optionally substituted by one or more

substituents which may be the same or different, and are as defined herein. The nitrogen or sulphur atom of the heterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide.

[0029] "Heterocyclyl" as used herein includes by way of example and not limitation those described in Paquette, Leo A. ; "Principles of Modern Heterocyclic Chemistry" (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and "J. Am. Chem. Soc. ", 82:5566 (1960). Exemplary monocyclic heterocyclyl rings include, but are not limited to, piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

[0030] "Heteroaryl" denotes an aromatic monocyclic or multicyclic ring system of about 5 to about 10 atoms, in which one or more of the atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur. Ring sizes of rings of the ring system include 5 to 6 ring atoms. The "heteroaryl" may also be substituted by one or more substituents which may be the same or different, and are as defined herein. The designation of the aza, oxa or thia as a prefix before heteroaryl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. A nitrogen atom of a heteroaryl may be optionally oxidized to the corresponding N-oxide. Heteroaryl as used herein includes by way of example and not limitation those described in Paquette, Leo A. ; "Principles of Modern Heterocyclic Chemistry" (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and "J. Am. Chem. Soc. ", 82:5566 (1960). Exemplary heteroaryl and substituted heteroaryl groups include, but are not limited to, pyrazinyl, thienyl, isothiazolyl, oxazolyl, pyrazolyl, furazanyl, pyrrolyl, 1,2,4-thiadiazolyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridine, imidazo[2,1-b]thiazolyl, benzofurazanyl, azaindolyl, benzimidazolyl, benzothienyl, thienopyridyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, benzoazaindole, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, benzthiazolyl, dioxolyl, furanyl, imidazolyl, indolyl, indolizinyl, isoxazolyl, isoquinolinyl, isothiazolyl, , oxadiazolyl, oxazinyl, oxiranyl, piperazinyl, piperidinyl, pyranyl, pyrazinyl, pyridazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, pyrrolidinyl, quinazolinyl, quinolinyl, tetrazinyl, tetrazolyl,

1,3,4-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, thiatriazolyl, thiazinyl, thiazolyl, thienyl, 5-thioxo-1,2,4-diazolyl, thiomorpholino, thiophenyl, thiopyranyl, triazolyl and triazolonyl.

[0031] The phrase "fused" means, that the group, mentioned before "fused" is connected via two adjacent atoms to the ring system mentioned after "fused" to form a bicyclic system. For example, "heterocycloalkyl fused aryl" includes, but is not limited to, 2,3-dihydro-benzo[1,4]dioxine, 4*H*-benzo[1,4]oxazin-3-one, 3*H*-Benzooxazol-2-one and 3,4-dihydro-2*H*-benzo[*f*][1,4]oxazepin-5-one.

[0032] The term "amino" denotes the radical $-NH_2$ wherein one or both of the hydrogen atoms may be replaced by an optionally substituted hydrocarbon group. Exemplary amino groups include, but are not limited to, n-butylamino, tert-butylamino, methylpropylamino and ethyldimethylamino.

[0033] The term "cycloalkylalkyl" denotes a cycloalkyl-alkyl group wherein a cycloalkyl as described above is bonded through an alkyl, as defined above. Cycloalkylalkyl groups may contain a lower alkyl moiety. Exemplary cycloalkylalkyl groups include, but are not limited to, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopropylethyl, cyclopentylethyl, cyclohexylpropyl, cyclopropylpropyl, cyclopentylpropyl, and cyclohexylpropyl.

[0034] The term "arylalkyl" denotes an aryl group as described above bonded through an alkyl, as defined above.

[0035] The term "heteroarylalkyl" denotes a heteroaryl group as described above bonded through an alkyl, as defined above.

[0036] The term "heterocyclylalkyl," or "heterocycloalkylalkyl," denotes a heterocyclyl group as described above bonded through an alkyl, as defined above.

[0037] The terms "halogen", "halo", or "hal", as used herein alone or as part of another group, denote chlorine, bromine, fluorine, and iodine.

[0038] The term "haloalkyl" denotes a halo group as described above bonded though an alkyl, as defined above. Fluoroalkyl is an exemplary group.

[0039] The term "aminoalkyl" denotes an amino group as defined above bonded through an alkyl, as defined above.

[0040] The phrase "bicyclic fused ring system wherein at least one ring is partially saturated" denotes an 8- to 13-membered fused bicyclic ring group in which at least one of the rings is non-aromatic. The ring group has carbon atoms and optionally 1-4 heteroatoms independently selected from N, O and S. Illustrative examples include, but are not limited to, indanyl, tetrahydronaphthyl, tetrahydroquinolyl and benzocycloheptyl.

[0041] The phrase "tricyclic fused ring system wherein at least one ring is partially saturated" denotes a 9- to 18-membered fused tricyclic ring group in which at least one of the rings is non-aromatic. The ring group has carbon atoms and optionally 1-7 heteroatoms independently selected from N, O and S. Illustrative examples include, but are not limited to, fluorene, 10,11-dihydro-5H-dibenzo[a,d]cycloheptene and 2,2a,7,7a-tetrahydro-1H-cyclobuta[a]indene.

[0042] The term "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. Examples therefore may be, but are not limited to, sodium, potassium, choline, lysine, arginine or N-methyl-glucamine salts, and the like.

[0043] The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as, but not limited to, hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as, but not limited to, acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

[0044] The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two. Organic solvents include, but are not limited to, nonaqueous media like ethers, ethyl acetate, ethanol, isopropanol, or acetonitrile. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, 1990, p. 1445, the disclosure of which is hereby incorporated by reference.

[0045] The phrase "pharmaceutically acceptable" denotes those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio.

[0046] The phrase "pharmaceutically acceptable carrier" denotes media generally accepted in the art for the delivery of biologically active agents to mammals, e.g., humans. Such carriers are generally formulated according to a number of factors well within the purview of those of ordinary skill in the art to determine and account for. These include, without limitation: the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and, the therapeutic indication being targeted. Pharmaceutically acceptable carriers include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi-solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, e.g., stabilization of the active agent, well known to those of ordinary skill in the art. Non-limiting examples of a pharmaceutically acceptable carrier are hyaluronic acid and salts thereof, and microspheres (including, but not limited to poly(D,L)-lactide-co-glycolic acid copolymer (PLGA), poly(L-lactic acid) (PLA), poly(caprolactone (PCL) and bovine serum albumin (BSA)). Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources, e.g., Remington's Pharmaceutical Sciences,

17th ed., Mack Publishing Company, Easton, Pa., 1985, the contents of which are incorporated herein by reference.

[0047] Pharmaceutically acceptable carriers particularly suitable for use in conjunction with tablets include, for example, inert diluents, such as celluloses, calcium or sodium carbonate, lactose, calcium or sodium phosphate; disintegrating agents, such as croscarmellose sodium, cross-linked povidone, maize starch, or alginic acid; binding agents, such as povidone, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[0048] Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example celluloses, lactose, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with non-aqueous or oil medium, such as glycerin, propylene glycol, polyethylene glycol, peanut oil, liquid paraffin or olive oil.

[0049] The compositions of the invention may also be formulated as suspensions including a compound of the present invention in admixture with at least one pharmaceutically acceptable excipient suitable for the manufacture of a suspension. In yet another embodiment, pharmaceutical compositions of the invention may be formulated as dispersible powders and granules suitable for preparation of a suspension by the addition of suitable excipients.

[0050] Carriers suitable for use in connection with suspensions include suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth, gum acacia, dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*, lecithin), a condensation product of an alkylene oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethyleneoxycethanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene sorbitan

monooleate); and thickening agents, such as carbomer, beeswax, hard paraffin or cetyl alcohol. The suspensions may also contain one or more preservatives such as acetic acid, methyl and/or n-propyl p-hydroxy-benzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

[0051] Cyclodextrins may be added as aqueous solubility enhancers. Preferred cyclodextrins include hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of α-, β-, and γ-cyclodextrin. The amount of solubility enhancer employed will depend on the amount of the compound of the present invention in the composition.

[0052] The term "formulation" denotes a product comprising the active ingredient(s) and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical formulations of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutical carrier.

[0053] The term "N-oxide" denotes compounds that can be obtained in a known manner by reacting a compound of the present invention including a nitrogen atom (such as in a pyridyl group) with hydrogen peroxide or a peracid, such as 3-chloroperoxy-benzoic acid, in an inert solvent, such as dichloromethane, at a temperature between about -10-80°C, desirably about 0°C.

[0054] The term "polymorph" denotes a form of a chemical compound in a particular crystalline arrangement. Certain polymorphs may exhibit enhanced thermodynamic stability and may be more suitable than other polymorphic forms for inclusion in pharmaceutical formulations.

[0055] The compounds of the invention can contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers), enantiomers, or diastereomers. According to the invention, the chemical structures depicted herein, and therefore the compounds of the invention, encompass all of the corresponding enantiomers and stereoisomers, that is, both the stereomerically pure form

(e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures.

[0056] The term "racemic mixture" denotes a mixture that is about 50% of one enantiomer and about 50% of the corresponding enantiomer relative to all chiral centers in the molecule. Thus, the invention encompasses all enantiomerically-pure, enantiomerically-enriched, and racemic mixtures of compounds of Formulas (I) through (VI).

[0057] Enantiomeric and stereoisomeric mixtures of compounds of the invention can be resolved into their component enantiomers or stereoisomers by well-known methods. Examples include, but are not limited to, the formation of chiral salts and the use of chiral or high performance liquid chromatography "HPLC" and the formation and crystallization of chiral salts. See, e.g., Jacques, J., et al., Enantiomers, Racemates and Resolutions (Wiley-Interscience, New York, 1981); Wilen, S. H., et al., Tetrahedron 33:2725 (1977); Eliel, E. L., Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); Wilen, S. H., Tables of Resolving Agents and Optical Resolutions p. 268 (E. L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, Ind., 1972); Stereochemistry of Organic Compounds, Ernest L. Eliel, Samuel H. Wilen and Lewis N. Manda (1994 John Wiley & Sons, Inc.), and Stereoselective Synthesis A Practical Approach, Mihaly Nogradi (1995 VCH Publishers, Inc., NY, N.Y.). Enantiomers and stereoisomers can also be obtained from stereomerically- or enantiomerically-pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

[0058] "Substituted" is intended to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O) group, then 2 hydrogens on the atom are replaced.

[0059] Unless moieties of a compound of the present invention are defined as being unsubstituted, the moieties of the compound may be substituted. In addition to any substituents provided above, the moieties of the compounds of the present invention may be optionally substituted with one or more groups independently selected from:

C_1-C_4 alkyl;

C_2-C_4 alkenyl;

C_2-C_4 alkynyl;

CF_3;

halo;

OH;

O-(C_1-C_4 alkyl);

OCH_2F;

$OCHF_2$;

OCF_3;

ONO_2;

OC(O)-(C_1-C_4 alkyl);

OC(O)-(C_1-C_4 alkyl);

OC(O)NH-(C_1-C_4 alkyl);

OC(O)N(C_1-C_4 alkyl)$_2$;

OC(S)NH-(C_1-C_4 alkyl);

OC(S)N(C_1-C_4 alkyl)$_2$;

SH;

S-(C_1-C_4 alkyl);

S(O)-(C_1-C_4 alkyl);

S(O)$_2$-(C_1-C_4 alkyl);

SC(O)-(C_1-C_4 alkyl);

$SC(O)O-(C_1-C_4\ alkyl)$;

NH_2;

$N(H)-(C_1-C_4\ alkyl)$;

$N(C_1-C_4\ alkyl)_2$;

$N(H)C(O)-(C_1-C_4\ alkyl)$;

$N(CH_3)C(O)-(C_1-C_4\ alkyl)$;

$N(H)C(O)-CF_3$;

$N(CH_3)C(O)-CF_3$;

$N(H)C(S)-(C_1-C_4\ alkyl)$;

$N(CH_3)C(S)-(C_1-C_4\ alkyl)$;

$N(H)S(O)_2-(C_1-C_4\ alkyl)$;

$N(H)C(O)NH_2$;

$N(H)C(O)NH-(C_1-C_4\ alkyl)$;

$N(CH_3)C(O)NH-(C_1-C_4\ alkyl)$;

$N(H)C(O)N(C_1-C_4\ alkyl)_2$;

$N(CH_3)C(O)N(C_1-C_4\ alkyl)_2$;

$N(H)S(O)_2NH_2$);

$N(H)S(O)_2NH-(C_1-C_4\ alkyl)$;

$N(CH_3)S(O)_2NH-(C_1-C_4\ alkyl)$;

$N(H)S(O)_2N(C_1-C_4\ alkyl)_2$;

$N(CH_3)S(O)_2N(C_1-C_4\ alkyl)_2$;

$N(H)C(O)O-(C_1-C_4\ alkyl)$;

$N(CH_3)C(O)O-(C_1-C_4\ alkyl)$;

$N(H)S(O)_2O-(C_1-C_4\ alkyl)$;

$N(CH_3)S(O)_2O-(C_1-C_4\ alkyl)$;

$N(CH_3)C(S)NH-(C_1-C_4\ alkyl)$;

$N(CH_3)C(S)N(C_1-C_4\ alkyl)_2$;

$N(CH_3)C(S)O-(C_1-C_4\ alkyl)$;

$N(H)C(S)NH_2$;

NO_2;

CO_2H;

$CO_2-(C_1-C_4\ alkyl)$;

C(O)N(H)OH;

$C(O)N(CH_3)OH$:

$C(O)N(CH_3)OH$;

$C(O)N(CH_3)O-(C_1-C_4\ alkyl)$;

$C(O)N(H)-(C_1-C_4\ alkyl)$;

$C(O)N(C_1-C_4\ alkyl)_2$;

$C(S)N(H)-(C_1-C_4\ alkyl)$;

$C(S)N(C_1-C_4\ alkyl)_2$;

$C(NH)N(H)-(C_1-C_4\ alkyl)$;

$C(NH)N(C_1-C_4\ alkyl)_2$;

$C(NCH_3)N(H)$-(C_1-C_4 alkyl);

$C(NCH_3)N$(C_1-C_4 alkyl)$_2$;

C(O)-(C_1-C_4 alkyl);

C(NH)-(C_1-C_4 alkyl);

$C(NCH_3)$-(C_1-C_4 alkyl);

C(NOH)-(C_1-C_4 alkyl);

$C(NOCH_3)$-(C_1-C_4 alkyl);

CN;

CHO;

CH_2OH;

CH_2O-(C_1-C_4 alkyl);

CH_2NH_2;

$CH_2N(H)$-(C_1-C_4 alkyl);

CH_2N(C_1-C_4 alkyl)$_2$;

aryl;

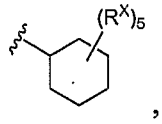
heteroaryl;

cycloalkyl; and

heterocyclyl.

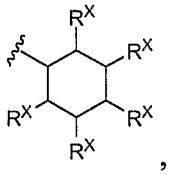
[0060] In some cases, a ring substituent may be shown as being connected to the ring by a bond extending from the center of the ring. The number of such substituents present on a ring is indicated in subscript by a number. Moreover, the substituent may be present on any available ring atom, the available ring atom being any ring atom which bears a hydrogen

which the ring substituent may replace. For illustrative purposes, if variable R^X were defined as being:

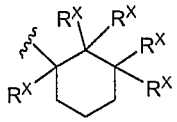


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this would indicate that R^X is a cyclohexyl ring bearing five R^X substituents. The R^X substituents may be bonded to any available ring atom. For example, among the configurations encompassed by this are configurations such as:

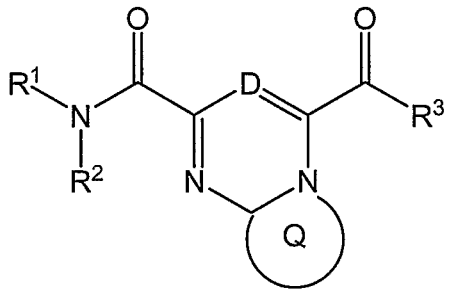


, and



These configurations are illustrative and are not meant to limit the scope of the invention in any way.

[0061] In one embodiment of the present invention, the amide containing heterobicyclic metalloprotease compounds may be represented by the general Formula (I):



Formula (I)

wherein:

R^1 is selected from hydrogen, alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl,

heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^3 is $NR^{20}R^{21}$;

R^4 in each occurrence is independently selected from R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-C(O)-NR^{11}-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted one or more times, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached

complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^{14} is independently selected from hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{20} is selected from hydrogen and alkyl, wherein alkyl is optionally substituted one or more times;

R^{21} is a bicyclic or tricyclic fused ring system, wherein at least one ring is partially saturated, and wherein the bicyclic or tricyclic fused ring system is optionally substituted one or more times;

R^{22} is selected from hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N{=}CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, SO_2R^{10} , $SO_2NR^{10}R^{11}$ and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{30} is selected from alkyl and $(C_0\text{-}C_6)$-alkyl-aryl, wherein alkyl and aryl are optionally substituted;

R^{50} in each occurrence is independently selected from hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{80} and R^{81} in each occurrence are independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted one or more times;

Q is a 5- or 6-membered ring selected from aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

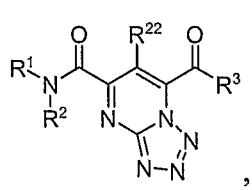
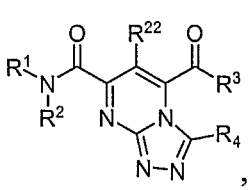
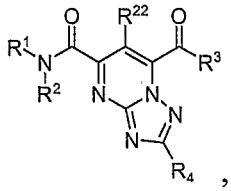
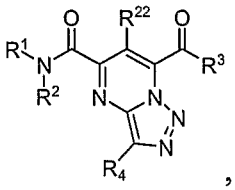
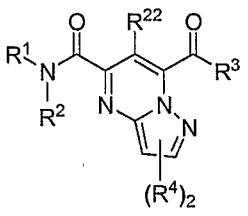
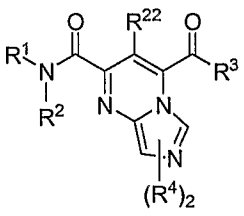
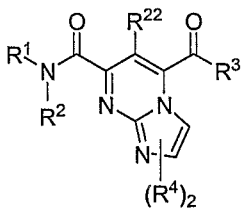
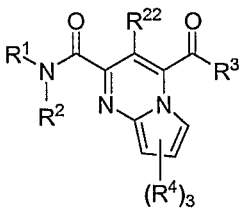
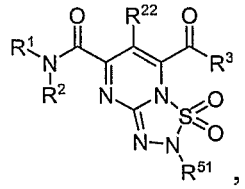
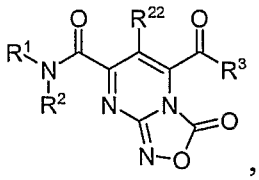
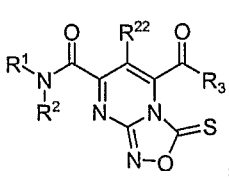
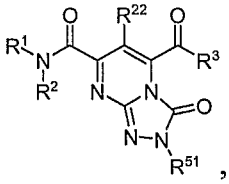
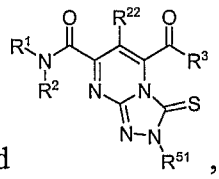
D is a member selected from CR^{22} and N;

x is selected from 0 to 2;

y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

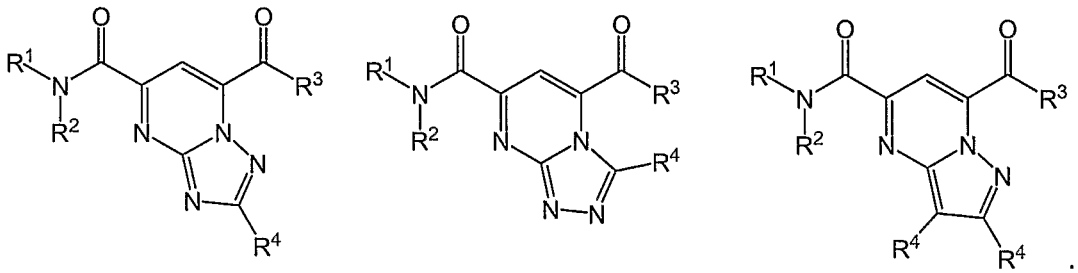
[0062] In another embodiment, compounds of Formula (I) may be selected from Group I(a):


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and ,

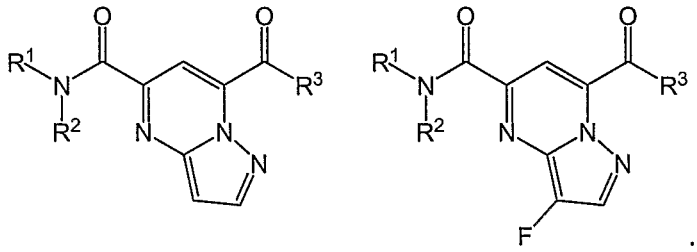
wherein:

R^{51} is independently selected from hydrogen, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and haloalkyl, wherein alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and haloalkyl are optionally substituted one or more times.

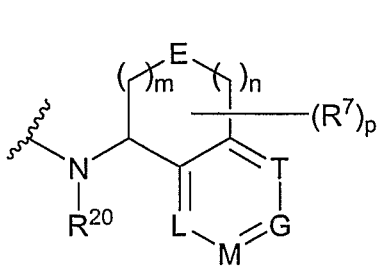
[0063] In still another embodiment, compounds of Formula (I) may be selected from:



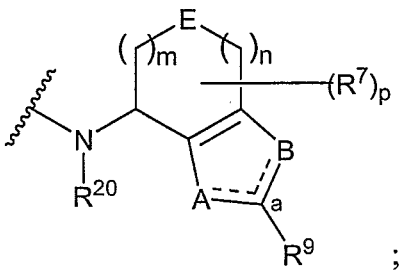
[0064] In yet another embodiment, compounds of Formula (I) may be selected from:



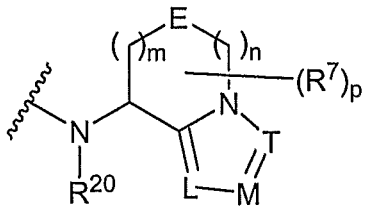
[0065] In some embodiments, R^3 of the compounds of Formula (I) may be selected from Substituent Group 1:



;



; and



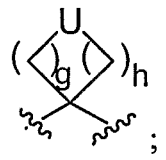
wherein:

R^5 is independently selected from hydrogen, alkyl, $C(O)NR^{10}R^{11}$, aryl, arylalkyl, $SO_2NR^{10}R^{11}$ and $C(O)OR^{10}$ wherein alkyl, aryl and arylalkyl are optionally substituted one or more times;

R^7 is independently selected from hydrogen, alkyl, cycloalkyl, halo, R^4 and $NR^{10}R^{11}$, wherein alkyl and cycloalkyl are optionally substituted one or more times, or optionally two R^7 groups together at the same carbon atom form =O, =S or $=NR^{10}$;

R^9 in each occurrence is independently selected from R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, CHF_2, CF_3, OR^{10}, $COOR^{10}$, $CH(CH_3)CO_2H$, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$P(O)_2OH$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=N\text{-}CN)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=N\text{-}CN)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=N\text{-}NO_2)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=N\text{-}NO_2)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2NR^{10}$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2NR^{10}$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $S(O)_2NR^{10}$-alkyl, $S(O)_2$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $(C_0\text{-}C_6)$-alkyl-$C(O)\text{-}NR^{11}$-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)\text{-}NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{11}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

E is selected from a bond, $CR^{10}R^{11}$, O, NR^5, S, S=O, $S(=O)_2$, C(=O), $N(R^{10})(C=O)$, $(C=O)N(R^{10})$, $N(R^{10})S(=O)_2$, $S(=O)_2N(R^{10})$, C=N-OR^{11}, $-C(R^{10}R^{11})C(R^{10}R^{11})-$, $-CH_2\text{-}W^1-$ and



;

W^1 is selected from O, NR^5, S, S=O, $S(=O)_2$, $N(R^{10})(C=O)$, $N(R^{10})S(=O)_2$ and $S(=O)_2N(R^{10})$;

U is selected from $C(R^5R^{10})$, NR^5, O, S, S=O and $S(=O)_2$;

A and B are independently selected from CR^9, CR^9R^{10}, NR^{10}, N, O and S;

G, L, M and T are independently selected from CR^9 and N;

g and h are independently selected from 0-2;

m and n are independently selected from 0-3, provided that:

when E is present, m and n are not both 3;

when E is $-CH_2-W^1-$, m and n are not 3; and

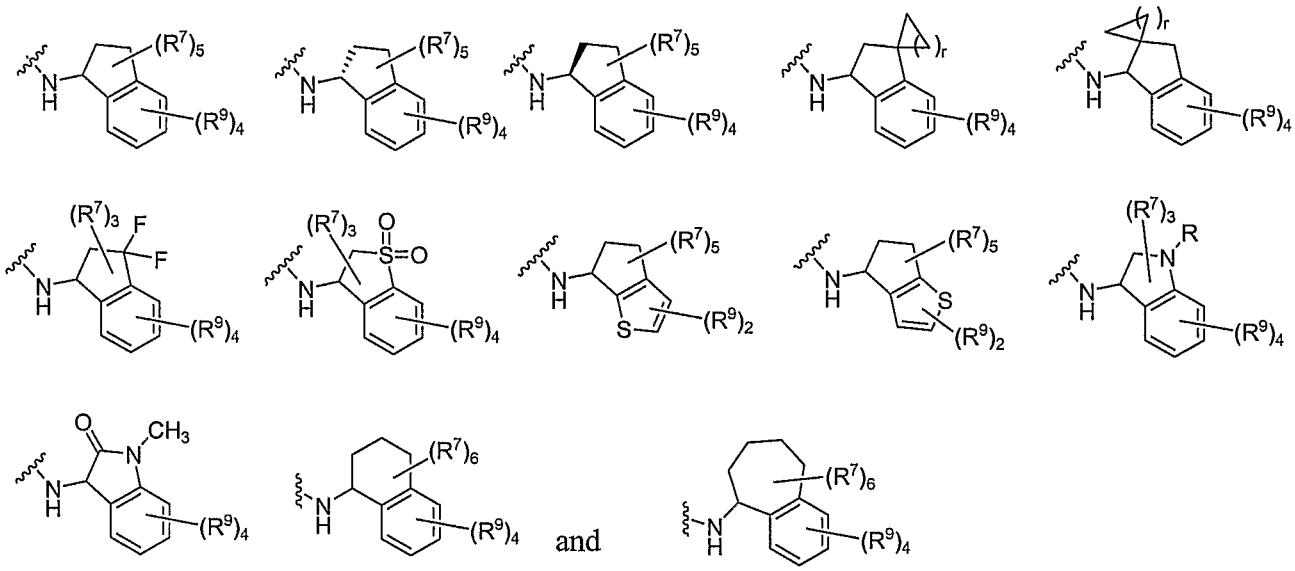
when E is a bond, m and n are not 0; and

p is selected from 0-6;

wherein the dotted line represents a double bond between one of: carbon "a" and A, or carbon "a" and B.

For example, in some embodiments, R^3 of the compounds of Group I(a) may be selected from Substituent Group 1 as defined hereinabove.

[0066] In some embodiments, R^3 of Formula (I) may be selected from Substituent Group I(2):



and

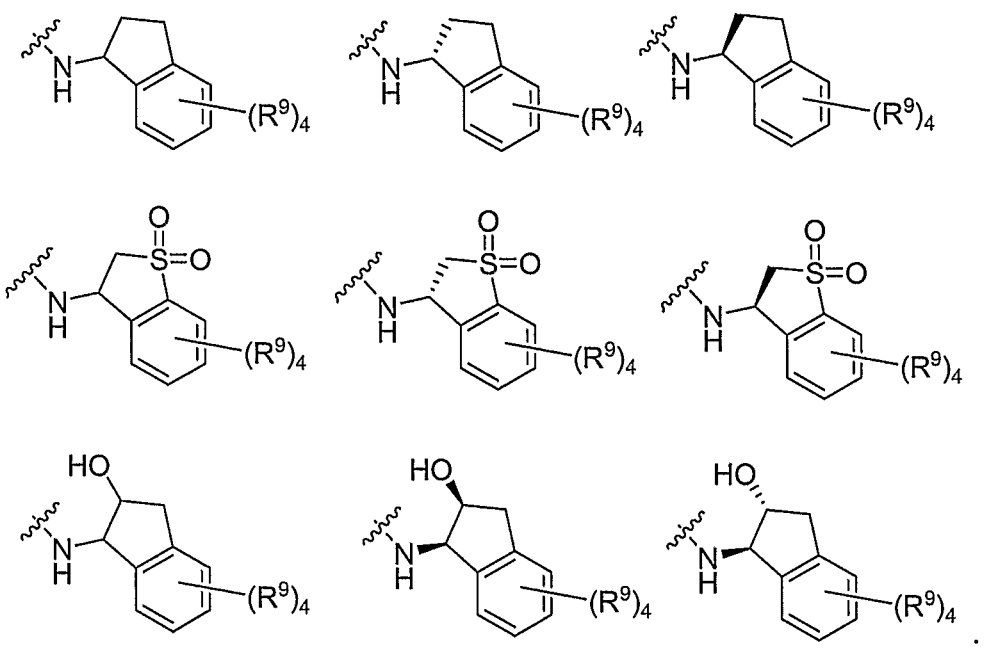
wherein:

R is selected from $C(O)NR^{10}R^{11}$, COR^{10}, $SO_2NR^{10}R^{11}$, SO_2R^{10}, $CONHCH_3$ and $CON(CH_3)_2$, wherein $C(O)NR^{10}R^{11}$, COR^{10}, $SO_2NR^{10}R^{11}$, SO_2R^{10}, $CONHCH_3$ and $CON(CH_3)_2$ are optionally substituted one or more times; and

r is selected from 1-4.

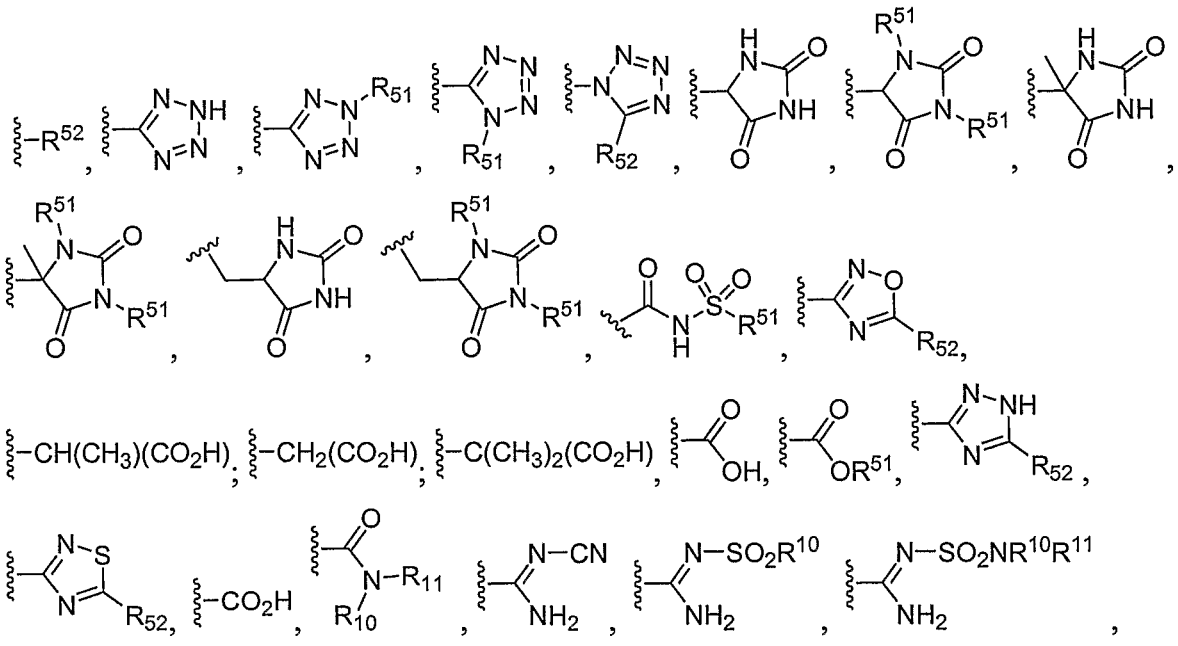
For example, in some embodiments, R^3 of the compounds of Group I(a) may be selected from Substituent Group 2, as defined hereinabove.

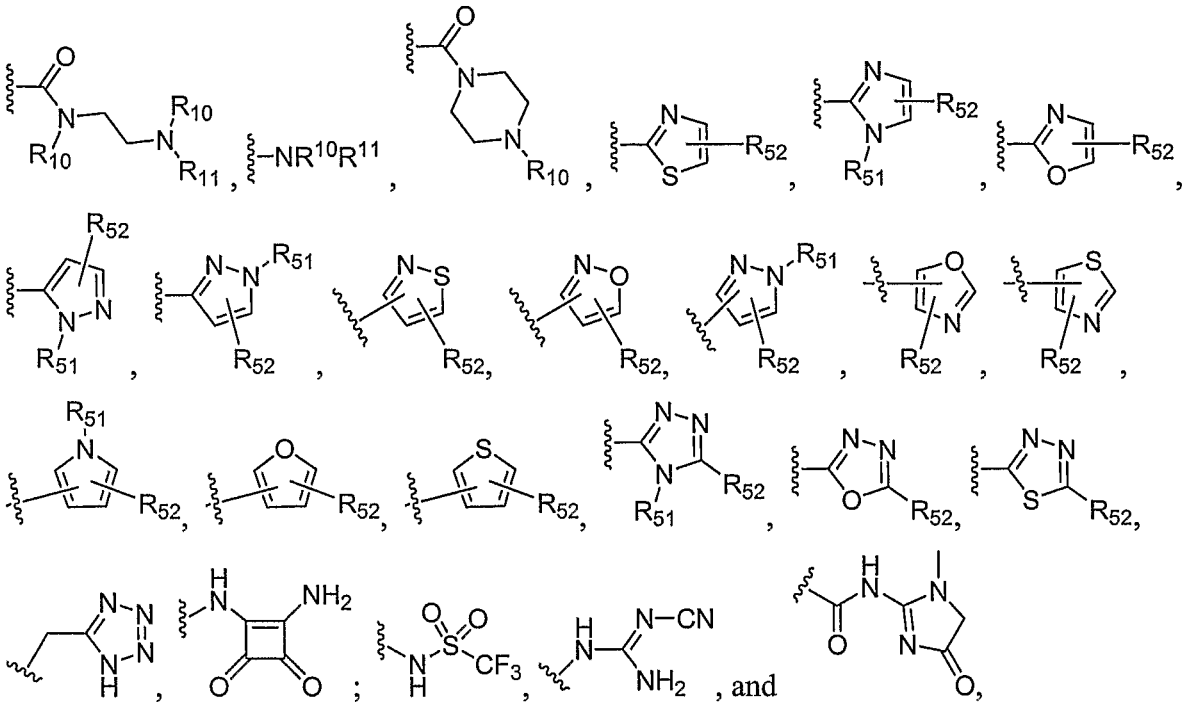
[0067] In yet a further embodiment, R^3 of Formula (I) may be selected from Substituent Group 3:



For example, in some embodiments, R^3 of the structures of Group I(a) may be selected from Substituent Group 3 as defined hereinabove.

[0068] In another embodiment, R^9 may be selected from Substituent Group 4:



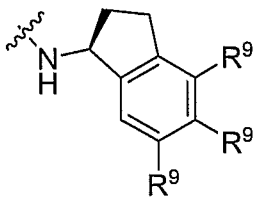


wherein:

R^{52} is selected from hydrogen, halo, CN, hydroxy, alkoxy, fluoroalkoxy, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, haloalkyl, $C(O)NR^{10}R^{11}$ and $SO_2NR^{10}R^{11}$, wherein alkoxy, fluoroalkoxy, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, and haloalkyl are optionally substituted one or more times.

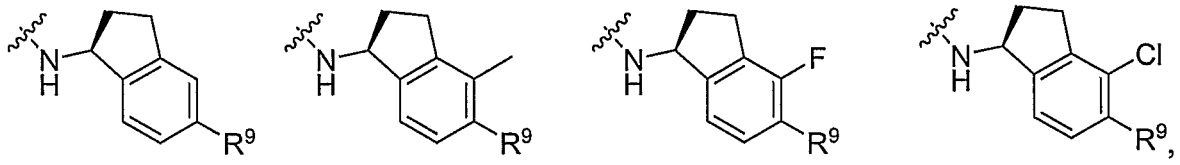
For example, in some embodiments, R^9 of Substituent Group 3 may be selected from Substituent Group 4 as defined hereinabove.

[0069] In yet a further embodiment, R^3 of the structures of Formula (I) may be Substituent Group 16:

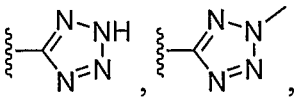
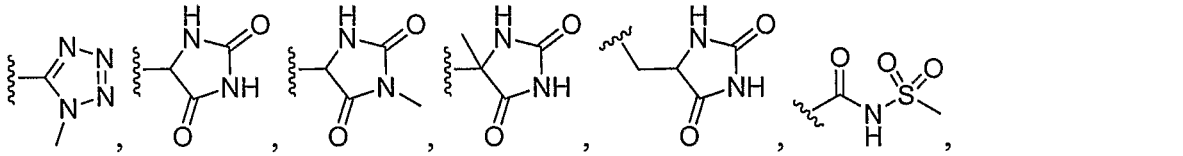
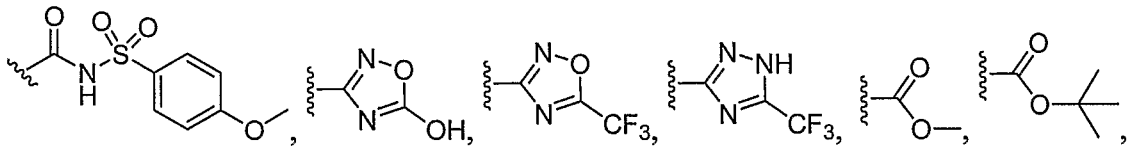
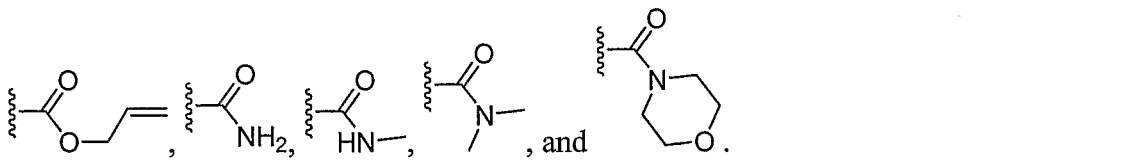
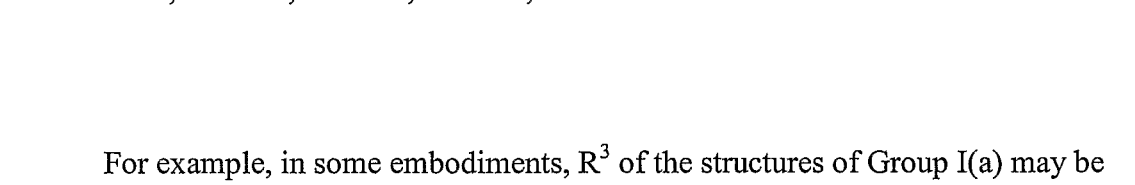


For example, in some embodiments, R^3 of the structures of Group I(a) may be selected from Substituent Group 16 as defined hereinabove.

[0070] In still a further embodiment, R^3 of Formula (I) may be selected from Substituent Group 5:

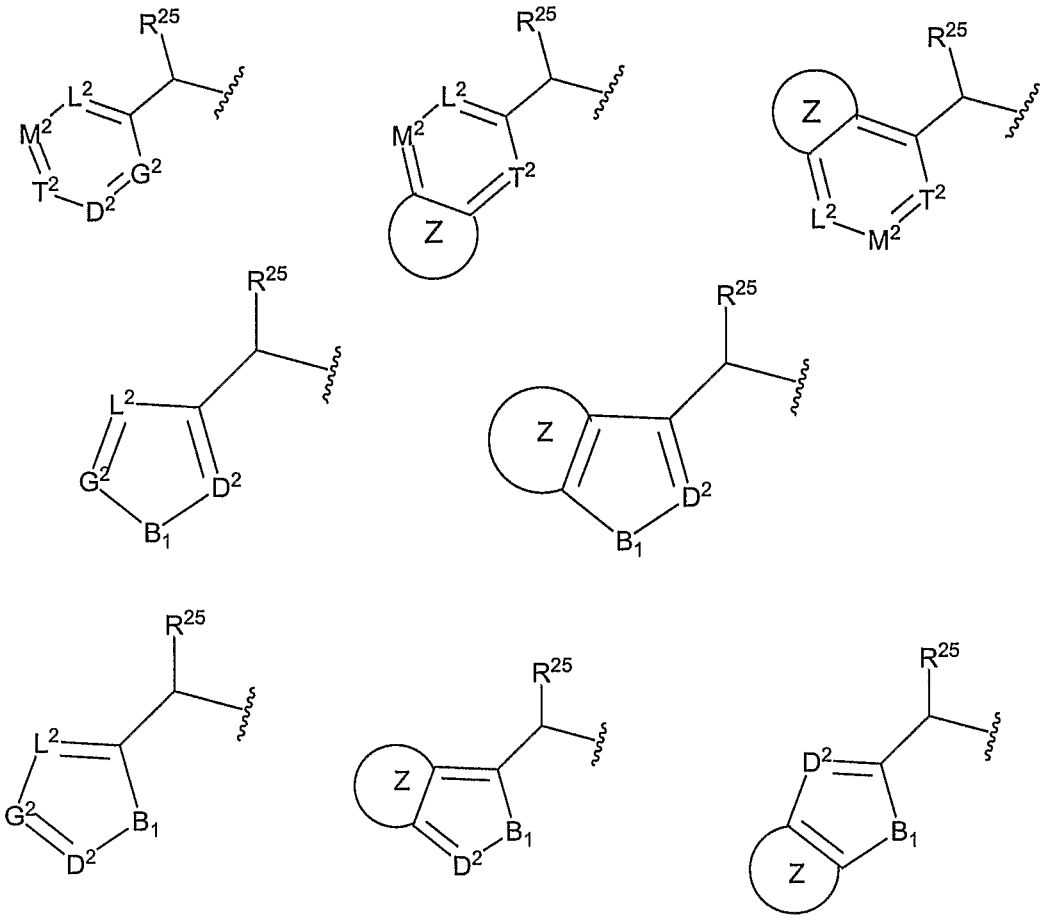


wherein:

R^9 is selected from hydrogen, fluoro, halo, CN, alkyl, CO_2H,  ,  ,  ,  ,  , and .

For example, in some embodiments, R^3 of the structures of Group I(a) may be selected from Substituent Group 5 as defined hereinabove.

[0071] In another embodiment, R^1 of Formula (I) may be selected from Substituent Group 6:



wherein:

R^{25} is selected from hydrogen, alkyl, cycloalkyl, $C(O)NR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

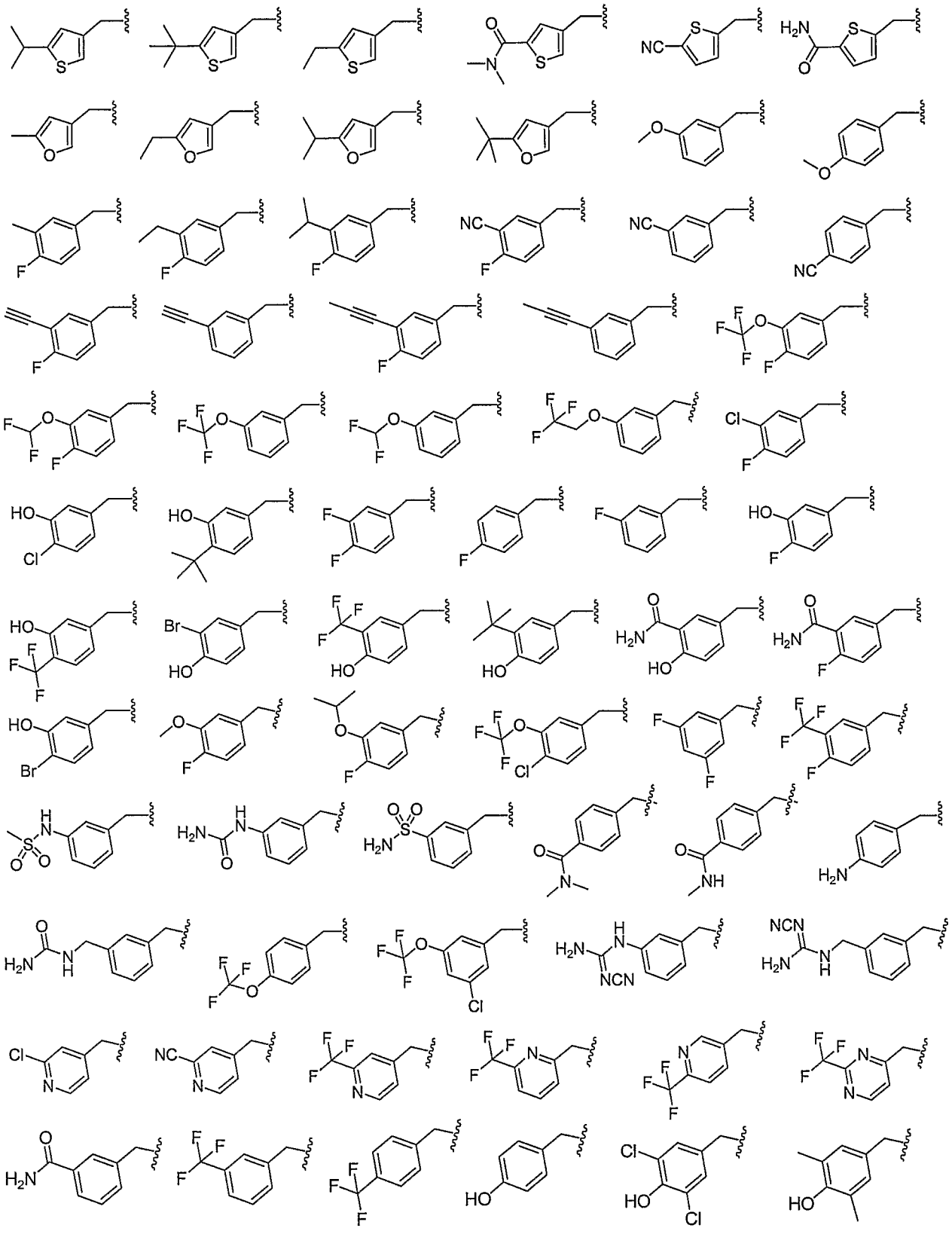
B_1 is selected from NR^{10}, O and S;

D^2, G^2, L^2, M^2 and T^2 are independently selected from CR^{18} and N; and

Z is a 5- to 8-membered ring selected from cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted one or more times.

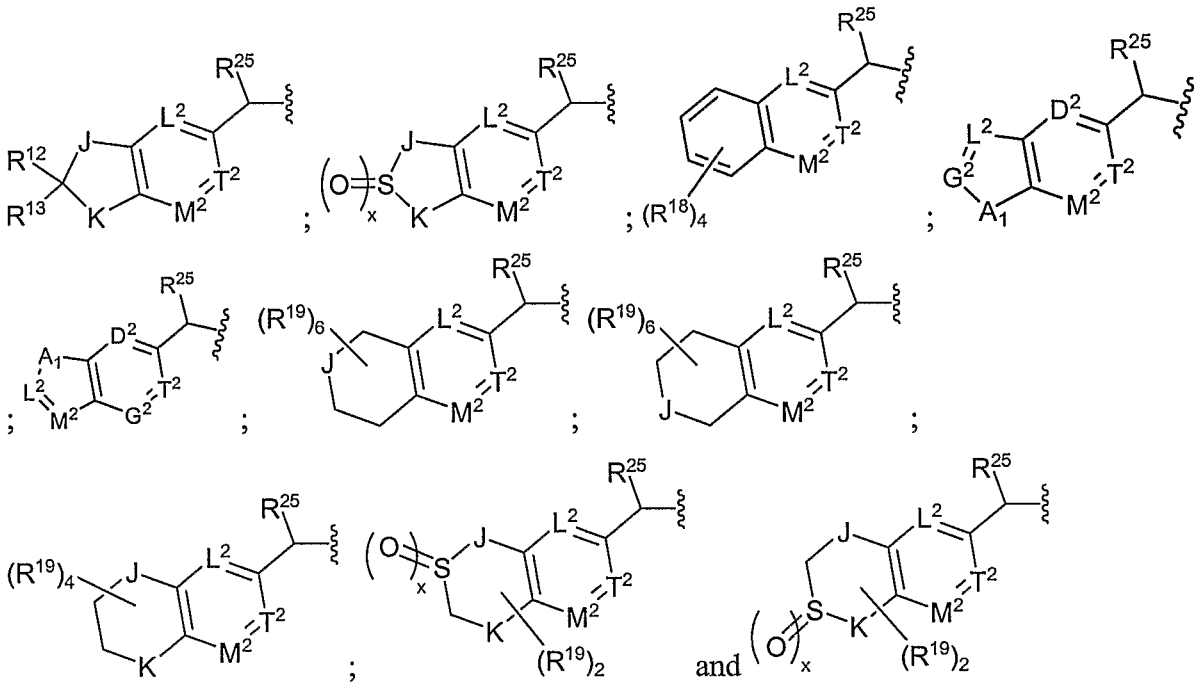
For example, in another embodiment, R^1 of the structures of Group I(a) may be selected from Substituent Group 6 as defined hereinabove.

[0072] In yet another embodiment, R^1 of the structures of Group I(a) may be selected from Substituent Group 7:



For example, in some embodiments, R^1 of the structures of Group I(a) may be selected from Substituent Group 7 as defined hereinabove.

[0073] In still another embodiment, R^1 of Formula (I) may be selected from Substituent Group 8:



wherein:

R^{12} and R^{13} are independently selected from hydrogen, alkyl and halo, wherein alkyl is optionally substituted one or more times, or optionally R^{12} and R^{13} together form =O, =S or $=NR^{10}$;

R^{18} is independently selected from the group consisting hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{19} is independently selected from the group consisting hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl,

aryl, and heteroaryl are optionally substituted one or more times, or optionally two R^{19} groups together at one carbon atom form =O, =S or $=NR^{10}$;

R^{25} is selected from hydrogen, alkyl, cycloalkyl, $C(O)NR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

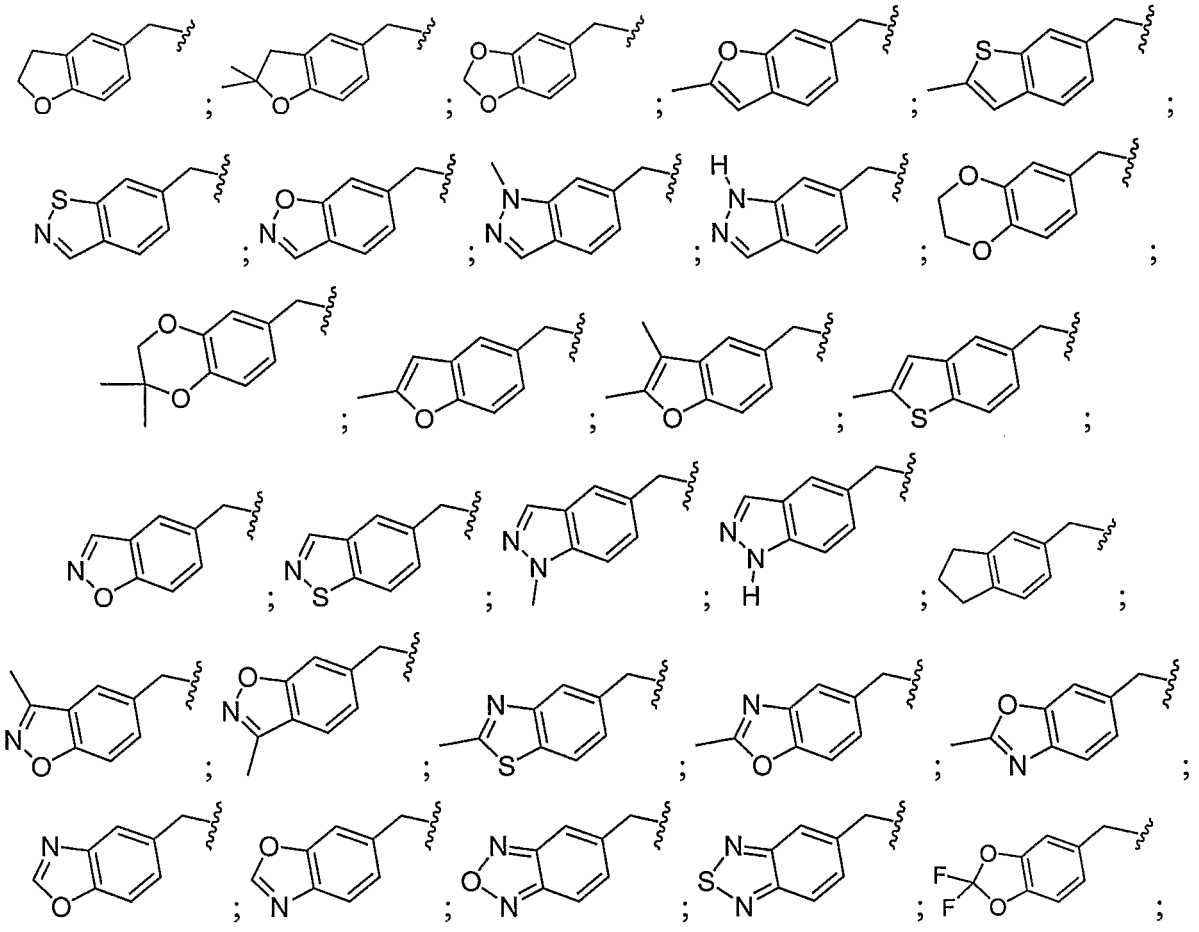
J and K are independently selected from $CR^{10}R^{18}$, NR^{10}, O and $S(O)_x$;

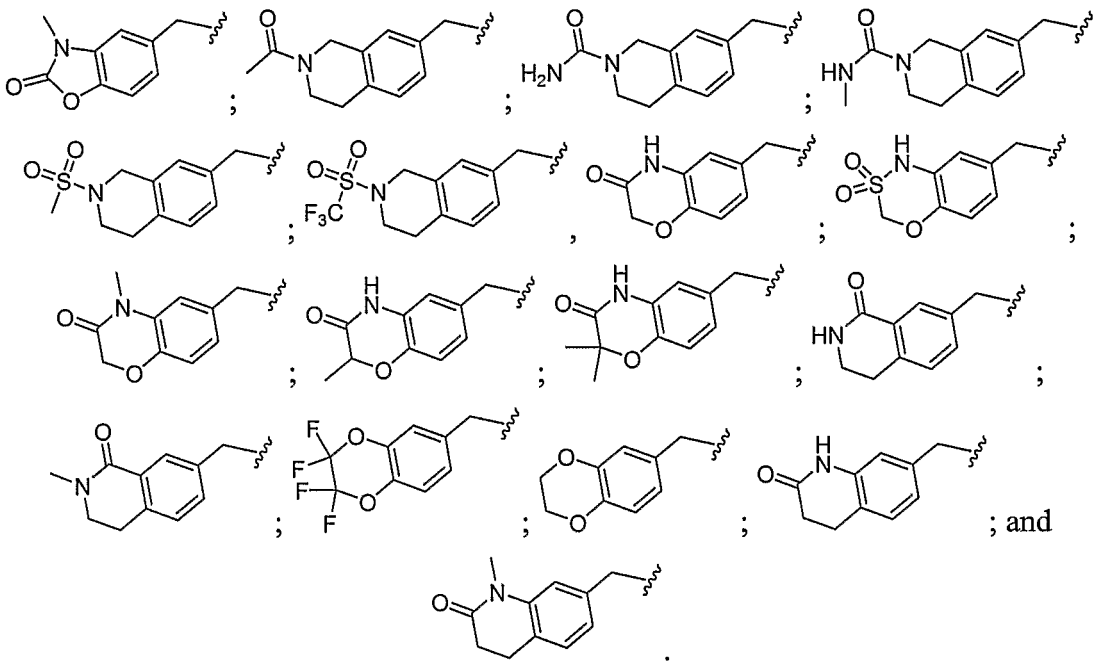
A_1 is selected from NR^{10}, O and S; and

D^2, G^2, L^2, M^2 and T^2 are independently selected from CR^{18} and N.

For example, some embodiments, R^1 of the structures of Group I(a) may be selected from Substituent Group 8 as defined hereinabove.

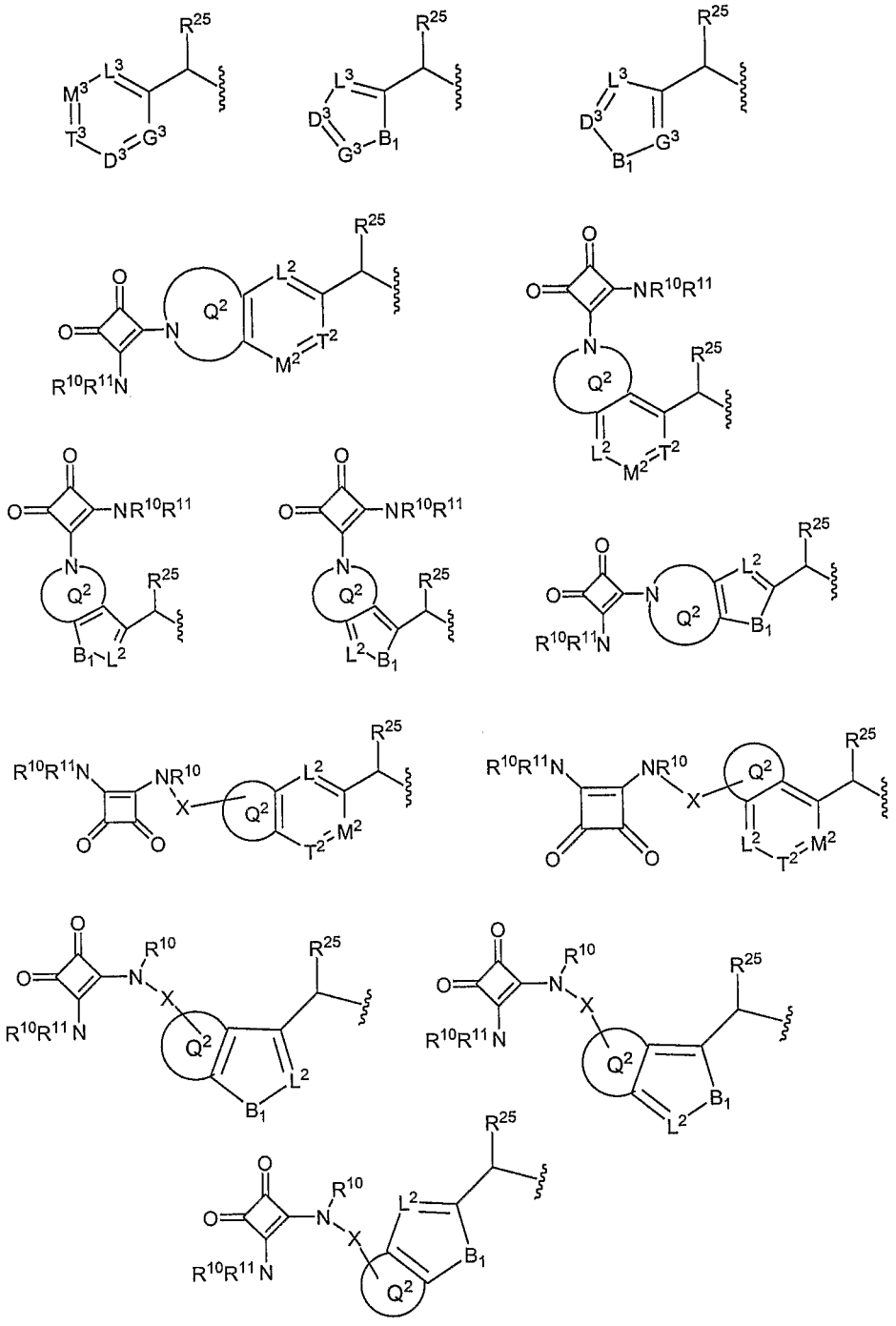
[0074] In a further embodiment, R^1 of Formula (I) may be selected from Substituent Group 9:





For example, in some embodiments, R^1 of the structures of Group I(a) may be selected from Substituent Group 9 as defined hereinabove.

[0075] In yet a further embodiment, R^1 of Formula (I) may be selected from Substituent Group 10:



wherein:

R^5 is independently selected from hydrogen, alkyl, $C(O)NR^{10}R^{11}$, aryl, arylalkyl, $SO_2NR^{10}R^{11}$ and $C(O)OR^{10}$ wherein alkyl, aryl and arylalkyl are optionally substituted one or more times;

R^{18} is independently selected from the group consisting hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10},

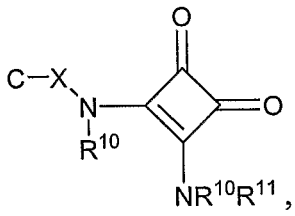
OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{19} is independently selected from the group consisting hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two R^{19} groups together at one carbon atom form =O, =S or $=NR^{10}$;

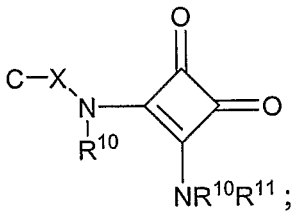
R^{25} is selected from hydrogen, alkyl, cycloalkyl, $CONR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl and haloalkyl are optionally substituted one or more times;

L^2, M^2, and T^2 are independently selected from CR^{18} and N;

L^3, M^3, T^3, D^3, and G^3 are independently selected from N, CR^{18}, and



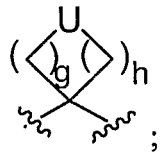
with the provision that one of L^3, M^3, T^3, D^3, and G^3 is



B_1 is selected from the group consisting of NR^{10}, O and S;

X is selected from a bond and $(CR^{10}R^{11})_wE(CR^{10}R^{11})_w$

E is selected from the group consisting of a bond, $CR^{10}R^{11}$, O, NR^5, S, S=O, $S(=O)_2$, C(=O), $N(R^{10})(C=O)$, $(C=O)N(R^{10})$, $N(R^{10})S(=O)_2$, $S(=O)_2N(R^{10})$, C=N-OR^{11}, $-C(R^{10}R^{11})C(R^{10}R^{11})-$, $-CH_2-W^1-$ and



;

W^1 is selected from the group consisting of O, NR^5, S, S=O, $S(=O)_2$, $N(R^{10})(C=O)$, $N(R^{10})S(=O)_2$ and $S(=O)_2N(R^{10})$;

U is selected from $C(R^5R^{10})$, NR^5, O, S, S=O, $S(=O)_2$;

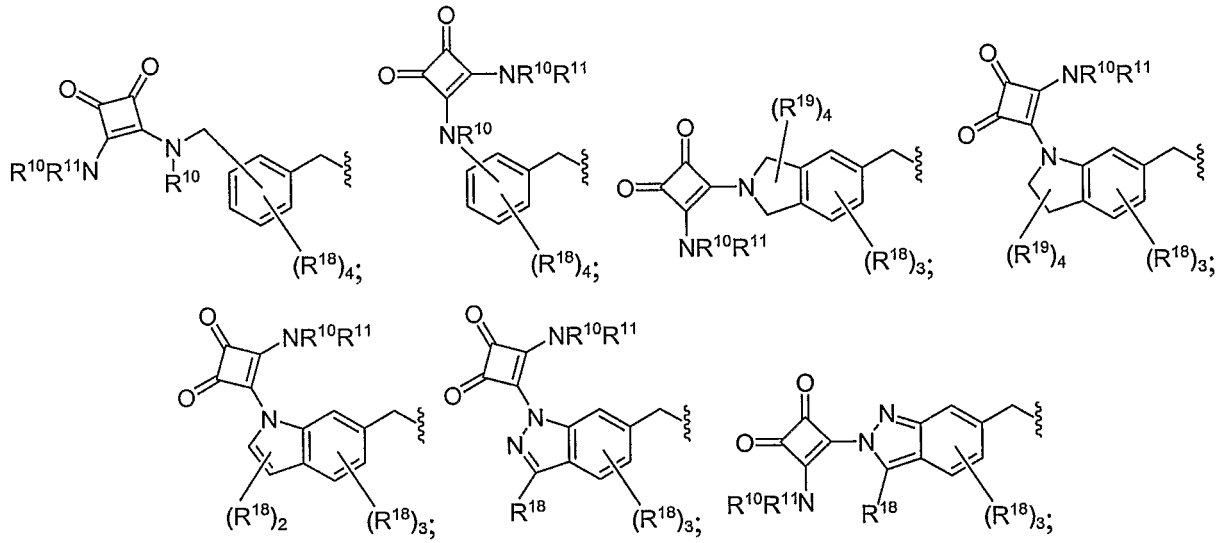
g and h are independently selected from 0-2;

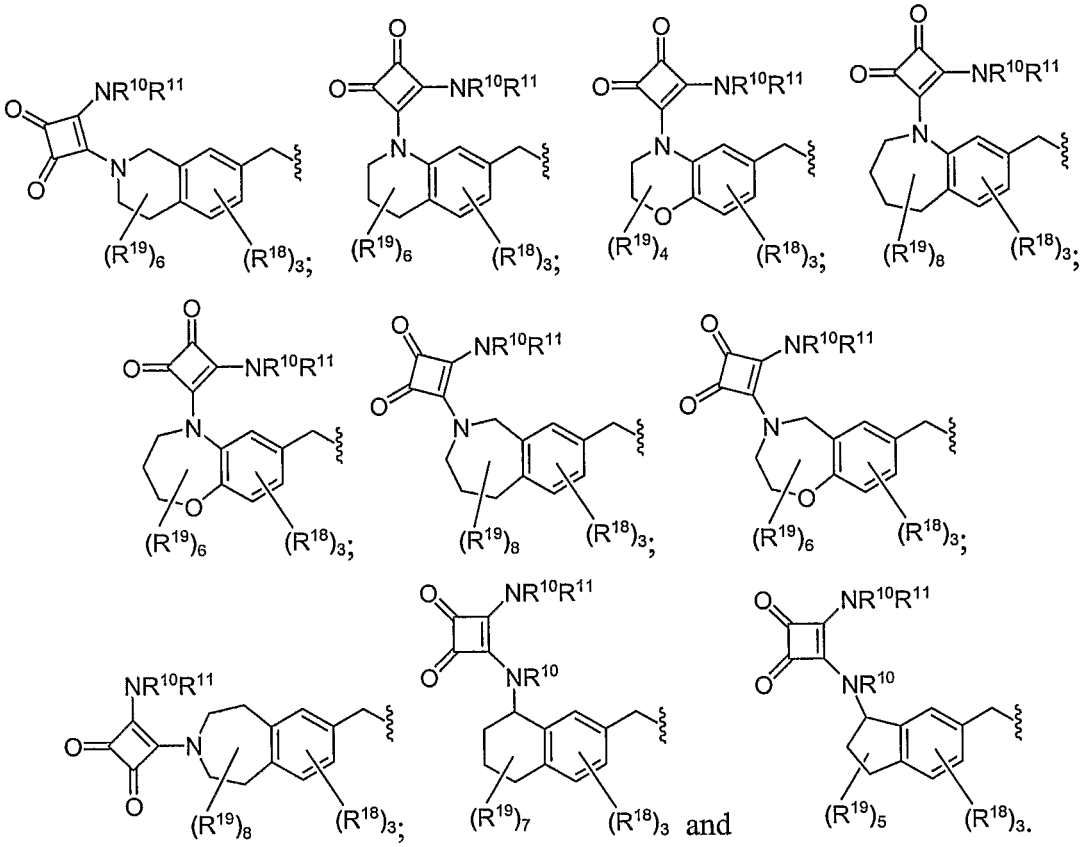
w is selected of 0-4; and

Q^2 is a 5- to 8-membered ring consisting of cycloalkyl, heterocycloalkyl, aryl, heteroaryl, which is optionally substituted one or more times with R^{19}.

[0076] For example, in some embodiments, R^1 of the structures of Group I(a) may be selected from Substituent Group 10 as defined herinabove.

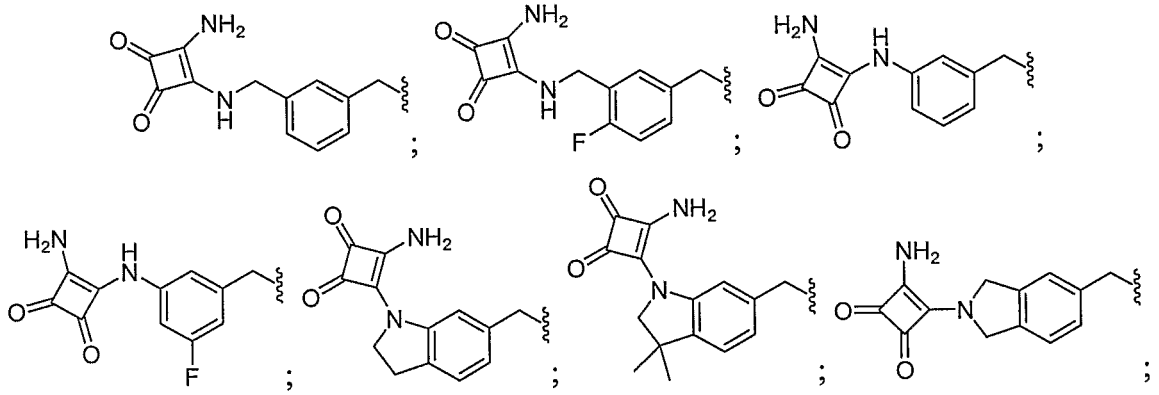
[0077] In still a further embodiment, R^1 of Formula (I) may be selected from Substituent Group 11:

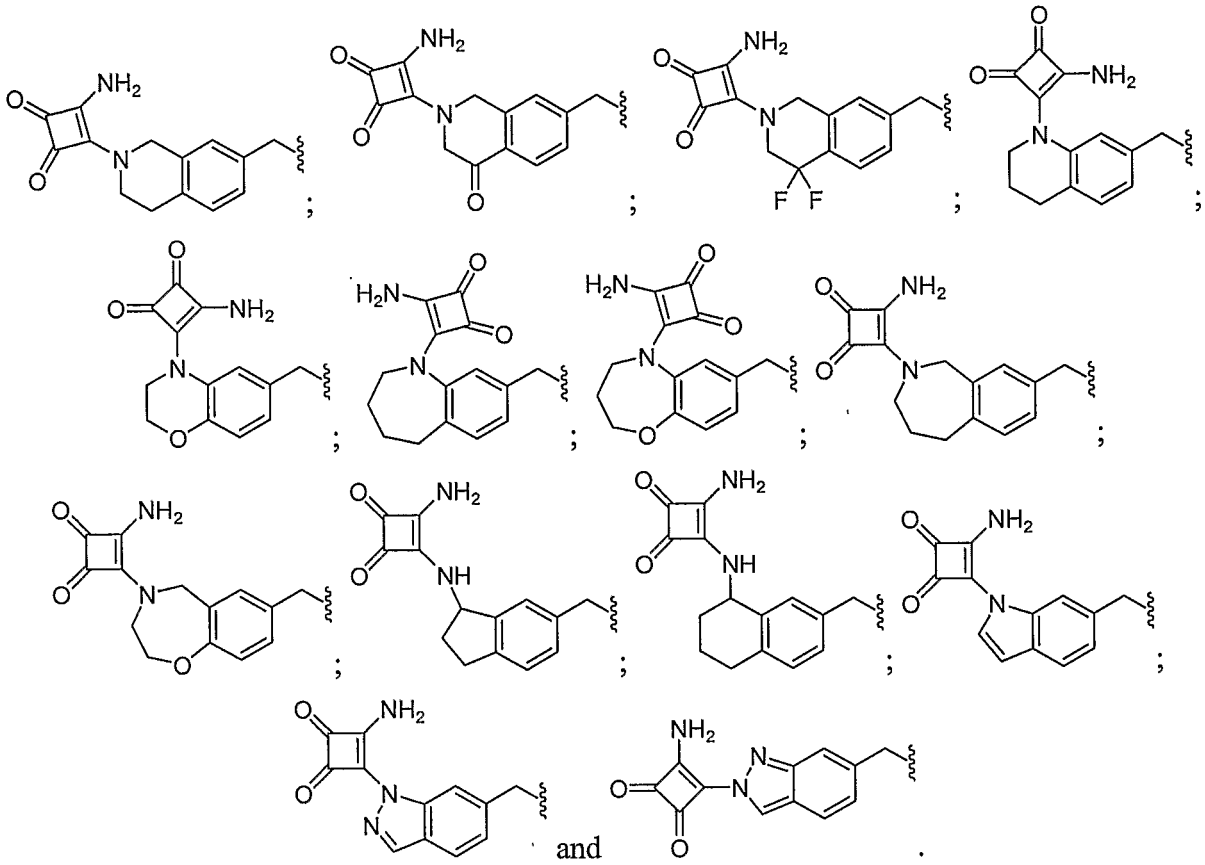




[0078] For example, in some embodiments, R^1 of the structures of Group I(a) may be selected from Substituent Group 11 as defined hereinabove.

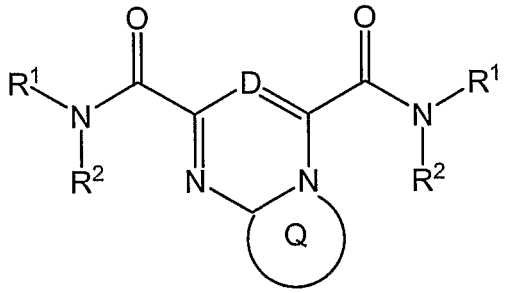
[0079] In another embodiment, R^1 of Formula (I) may be selected from Substituent Group 12:





For example, in some embodiments, R^1 of the structures of Group I(a) may be selected from Substituent Group 12 as defined hereinabove.

[0080] In yet another embodiment, the amide containing heterobicyclic metalloprotease compounds may be represented by the general Formula (II):



Formula (II)

and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof,

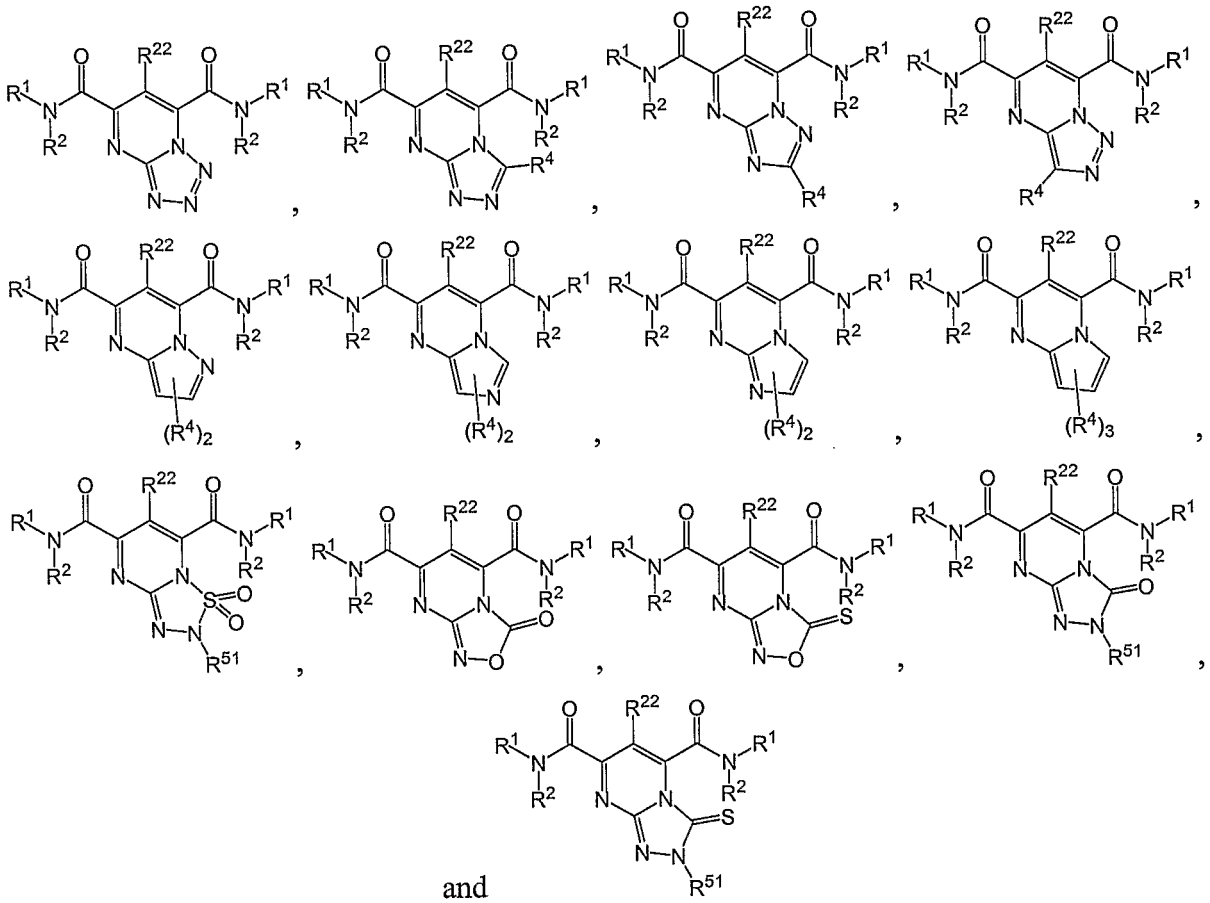
wherein:

R^1 in each occurrence may be the same or different and is as defined hereinabove;

R^2 in each occurrence may be the same or different and is as defined hereinabove; and

all remaining variables are as defined hereinabove.

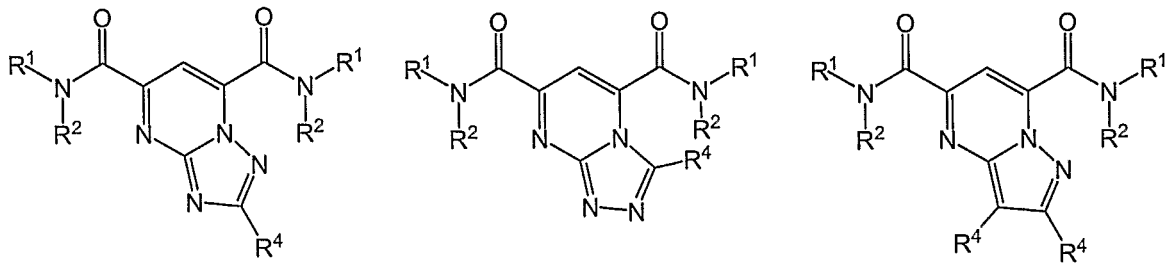
[0081] In still another embodiment, the compound of Formula (II) may be selected from Group II(a):



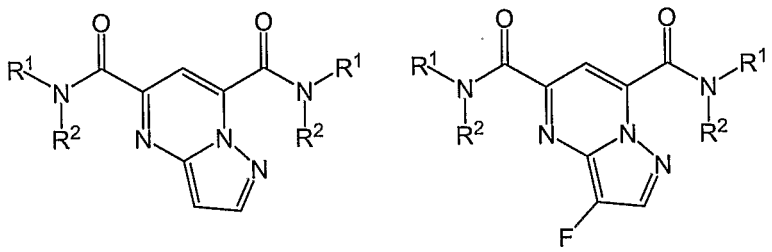
and

wherein all variables are as defined hereinabove.

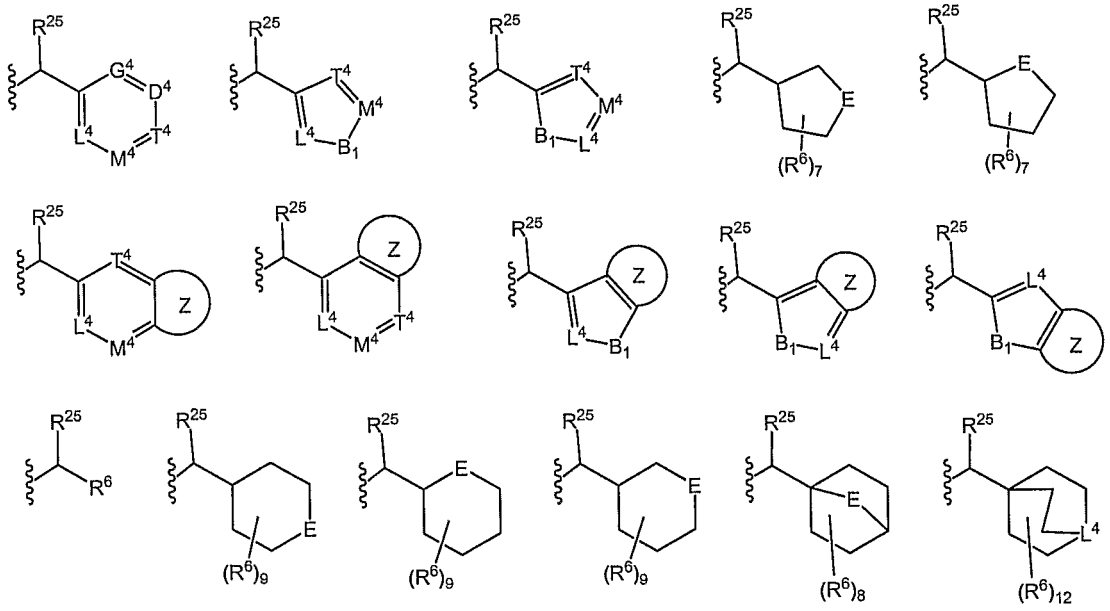
[0082] In a further embodiment, the compound of Formula (II) may be selected from:



[0083] In yet a further embodiment, the compound of Formula (II) may be selected from:



[0084] In still a further embodiment, at least one R^1 of Formula (II) may be selected from Substituent Group 13:



wherein:

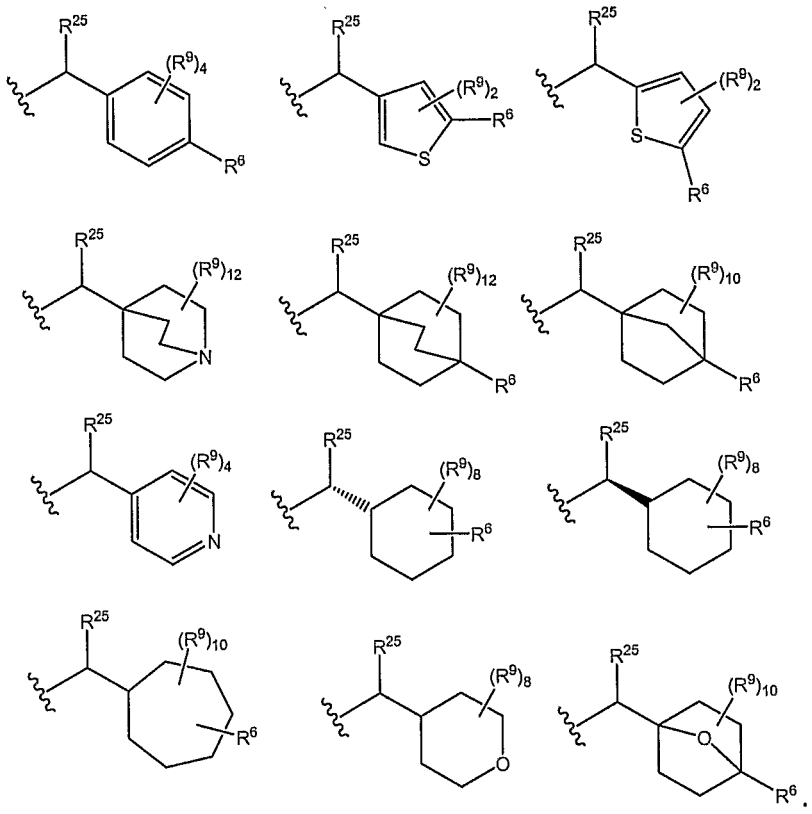
R^6 is selected from: R^9, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $C(O)OR^{10}$, $CH(CH_3)CO_2H$, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$P(O)_2OH$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=N\text{-}CN)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=N\text{-}CN)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=N\text{-}NO_2)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=N\text{-}NO_2)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2NR^{10}$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2NR^{10}$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $S(O)_2NR^{10}$-alkyl, $S(O)_2$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $(C_0\text{-}C_6)$-alkyl-$C(O)\text{-}NR^{11}$-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}\text{-}C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}\text{-}C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}\text{-}C(O)\text{-}NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}\text{-}S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}\text{-}S(O)_yR^{11}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^6 group is optionally substituted by one or more R^{14} groups;

D^4, G^4, L^4, M^4, and T^4 are independently selected from CR^6 or N; and

all remaining variables are as defined hereinabove.

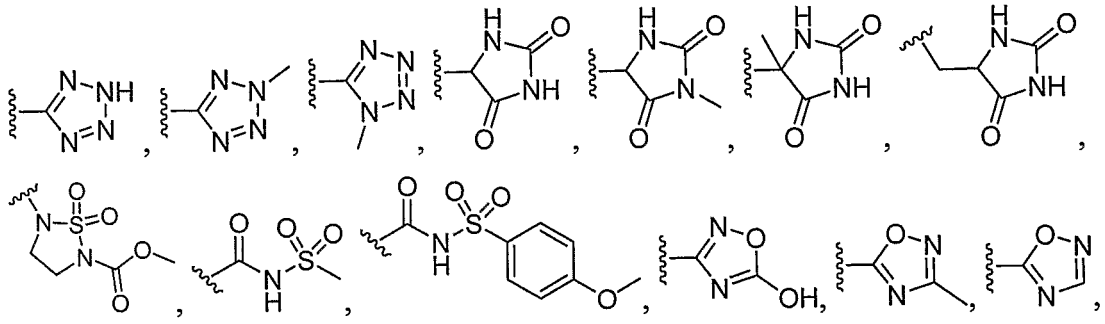
For example, in some embodiments, at least one R^1 of the structures of Group II(a) may independently be selected from Substituent Group 13 as defined hereinabove.

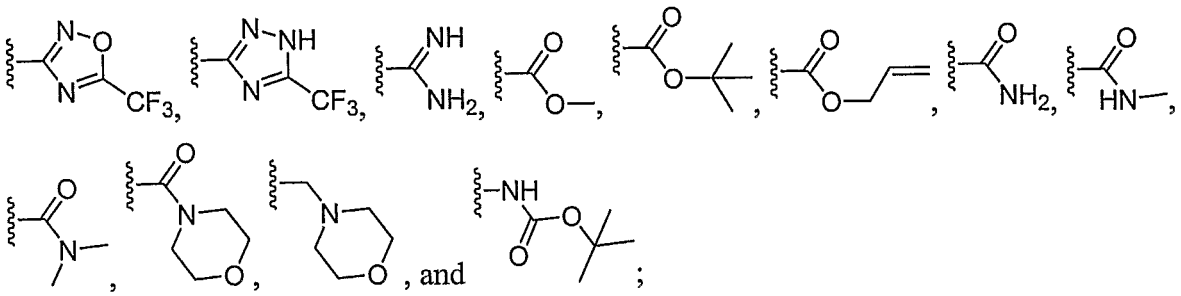
[0085] In another embodiment, at least one R^1 of Formula (II) may be selected from Substituent Group 14:



[0086] For example, in some embodiments, at least one R^1 of Group II(a) may independently be selected from Substituent Group 14 as defined hereinabove.

[0087] In yet another embodiment, R^6 of Substituent Group 14 may be selected from: hydrogen, halo, CN, OH, CH_2OH, CF_3, CHF_2, OCF_3, $OCHF_2$, $COCH_3$, SO_2CH_3, SO_2CF_3, SO_2NH_2, SO_2NHCH_3, $SO_2N(CH_3)_2$, NH_2, $NHCOCH_3$, $N(COCH_3)_2$, $NHCONH_2$, $NHSO_2CH_3$, alkoxy, alkyl, CO_2H,



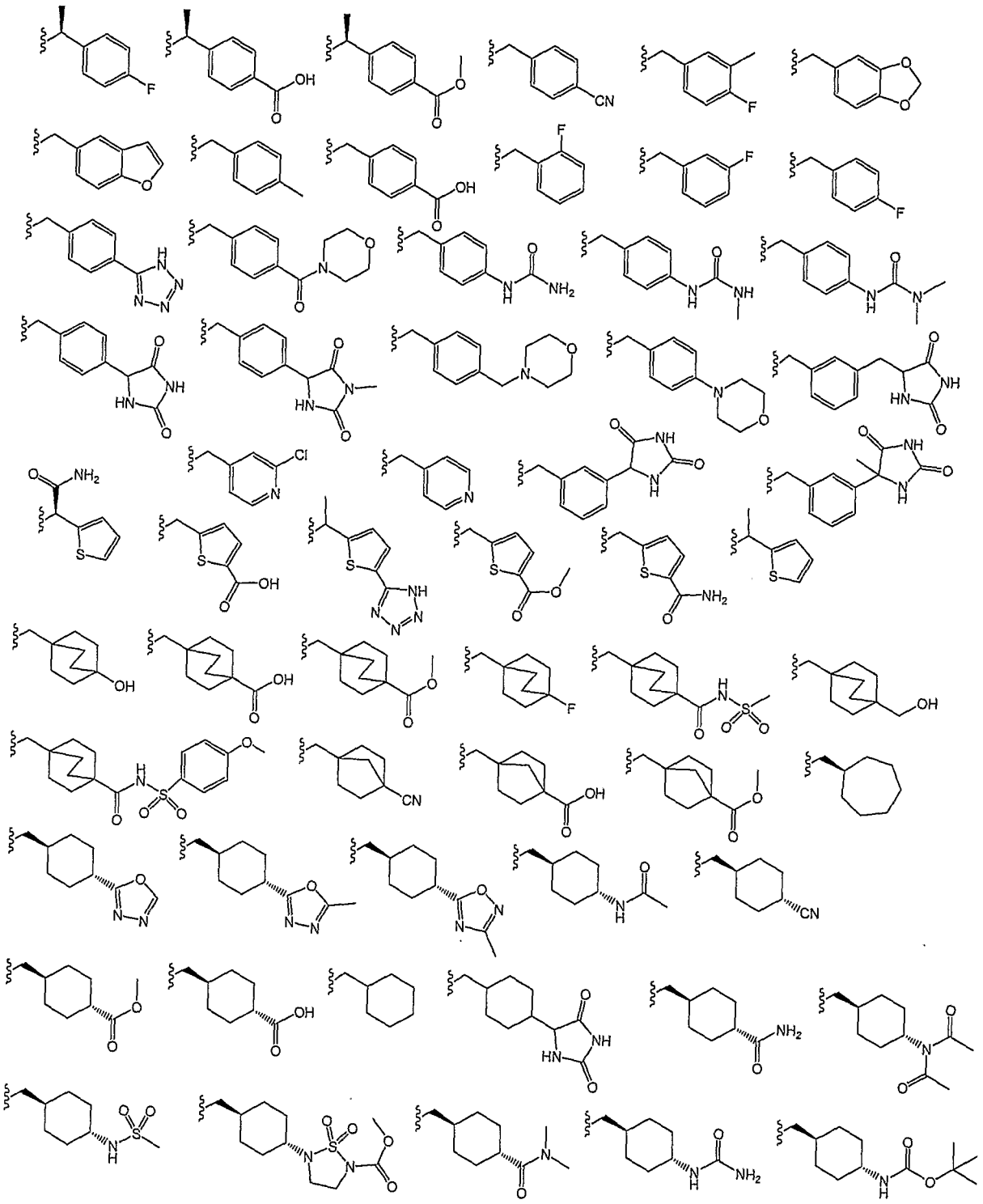


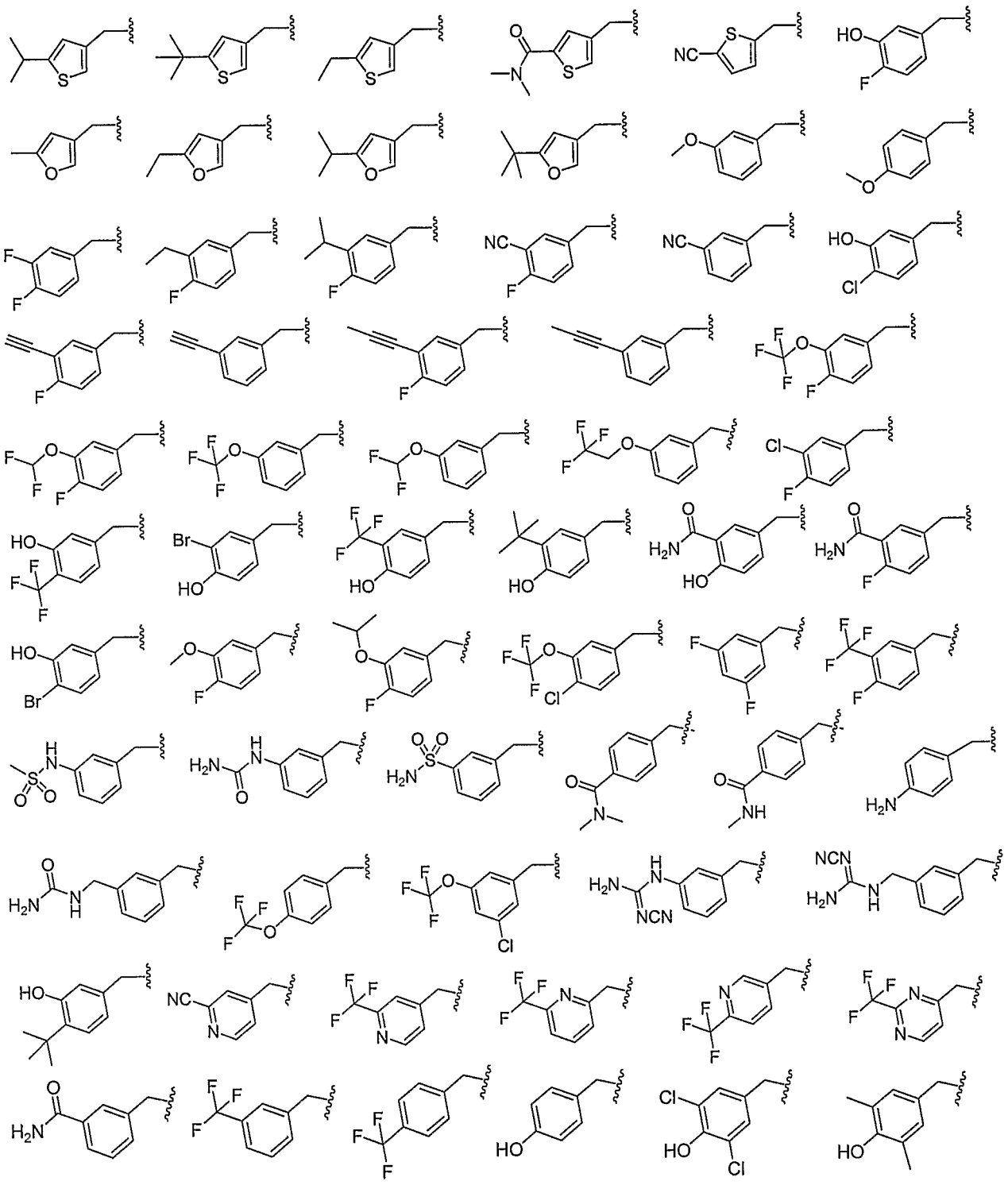
wherein

R^9 in each occurrence is independently selected of hydrogen, fluoro, chloro, CH_3, CF_3, CHF_2, OCF_3, and $OCHF_2$; and

R^{25} is selected of hydrogen, CH_3, COOMe, COOH, and $CONH_2$.

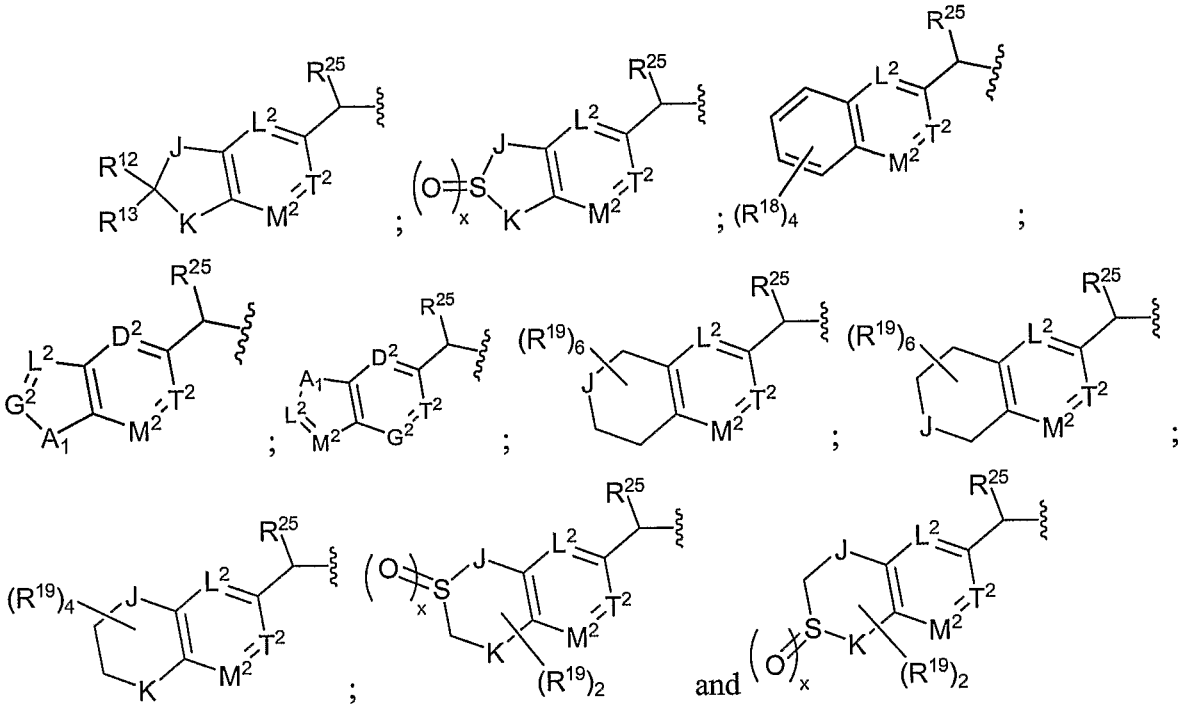
[0088] In yet another embodiment, at least one R^1 of Formula (II) may be selected from Substituent Group 15:





For example, in some embodiments, at least one R^1 of Group II(a) may be selected from Substituent Group 15 as defined hereinabove.

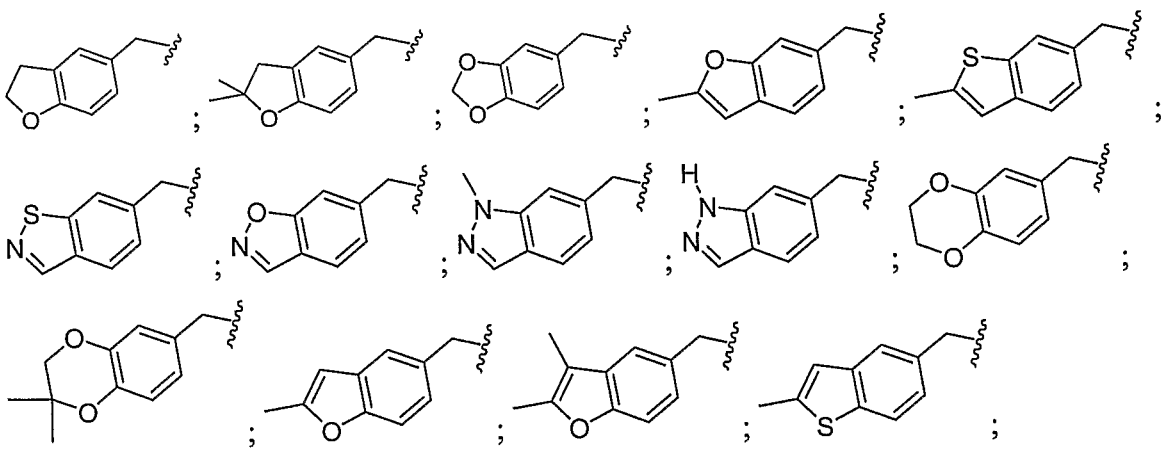
[0089] In still another embodiment, at least one R^1 of Formula (II) may be selected from Substituent Group 8:

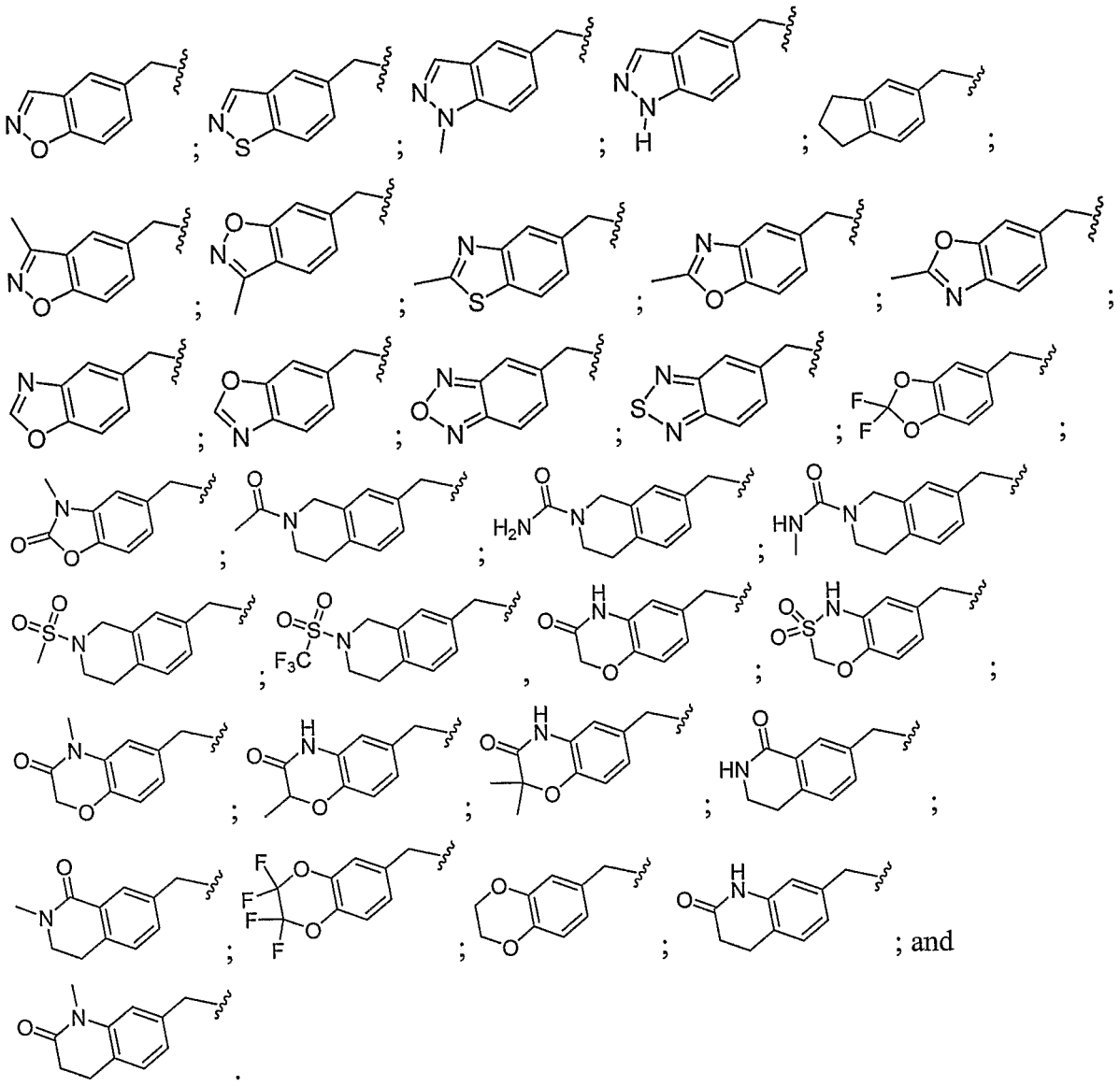


wherein all variables are as defined hereinabove.

For example, in some embodiments, at least one R^1 of Group II(a) may be selected from Substituent Group 8 as defined hereinabove.

[0090] In a further embodiment, at least one R^1 of Formula (II) may be selected from Substituent Group 9:



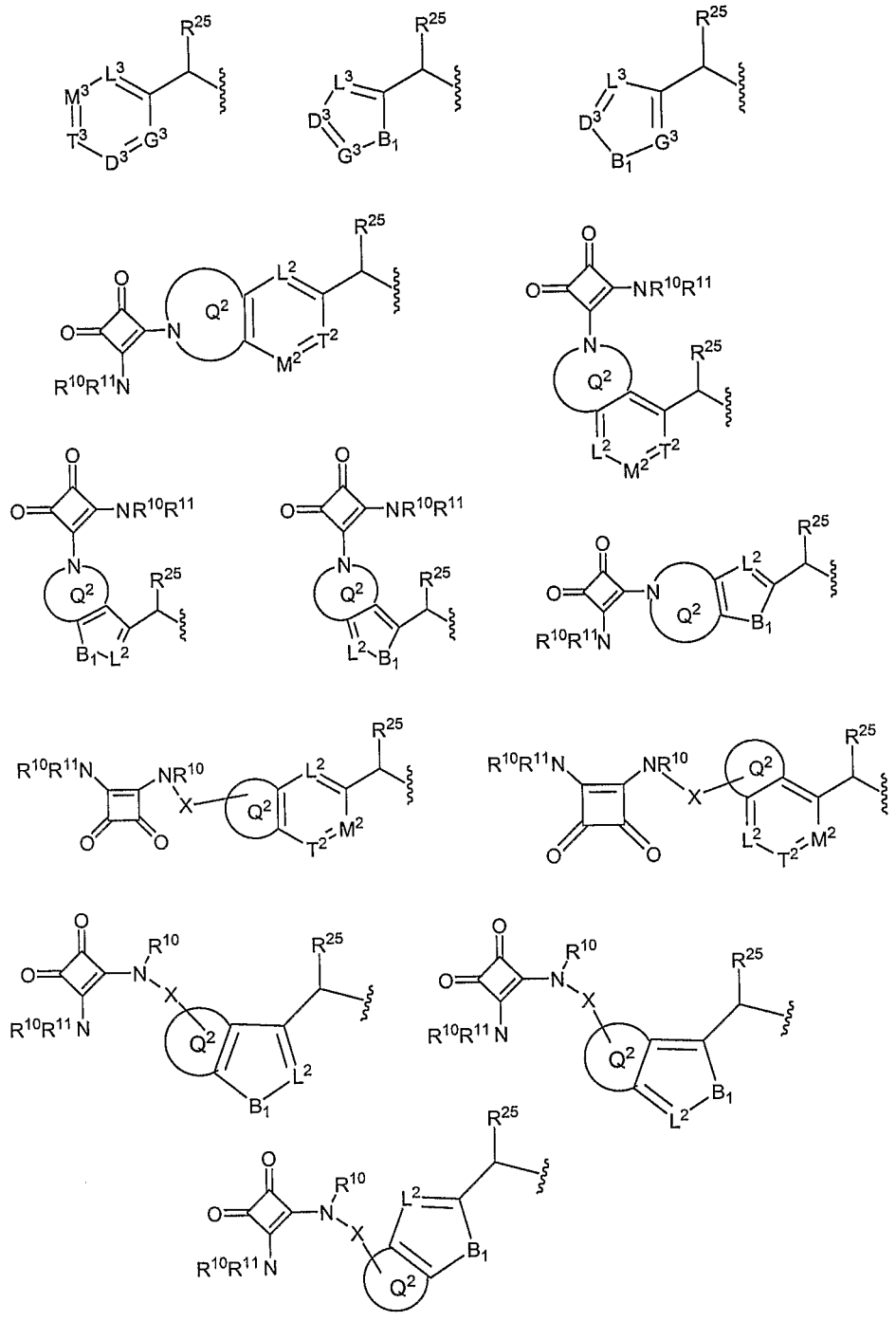


; and

.

[0091] For example, in some embodiments, at least one R^1 of Group II(a) may be selected from Substituent Group 9 as defined hereinabove.

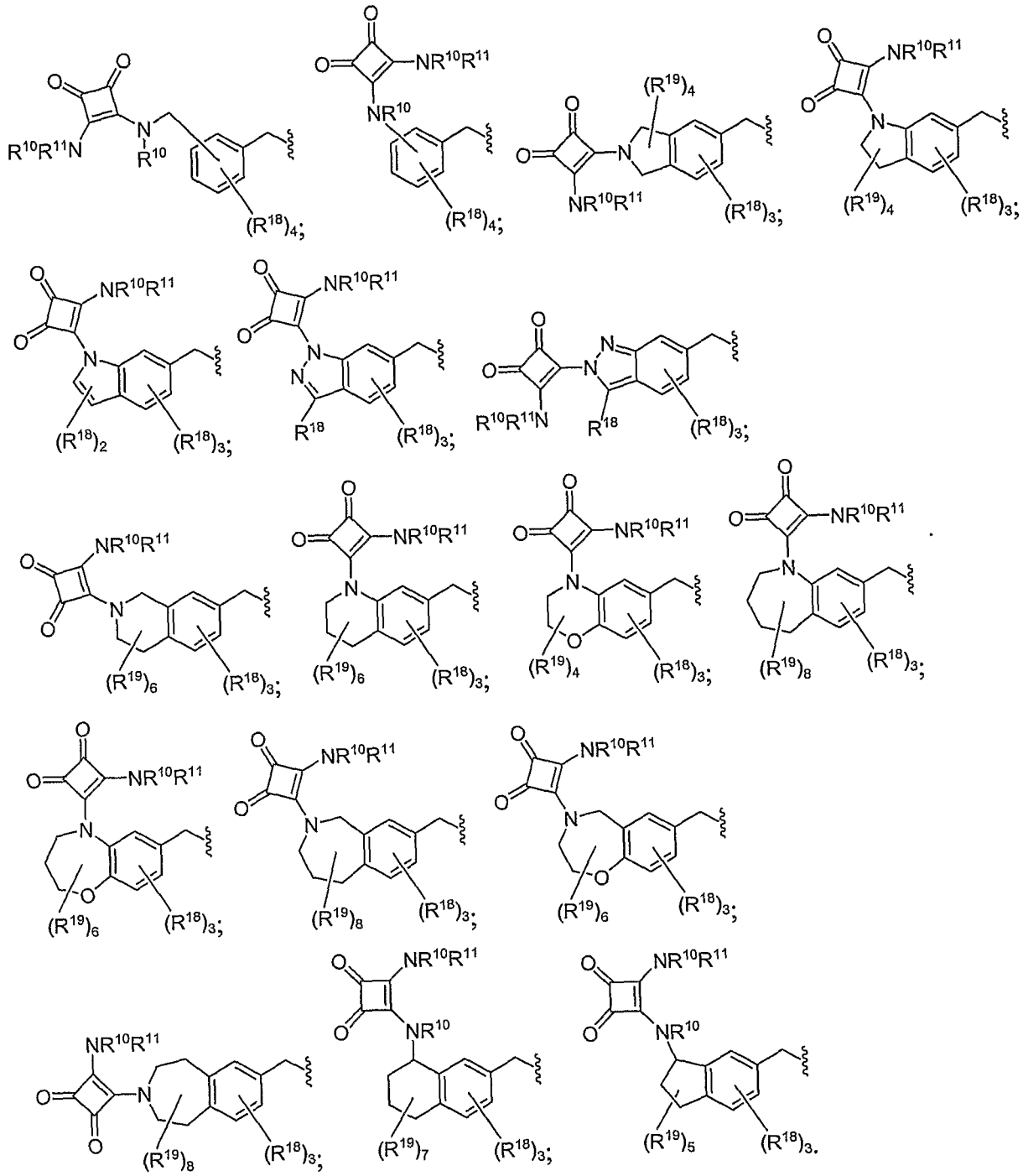
[0092] In yet a further embodiment, one R^1 of Formula (II) may be selected from Substituent Group 10:



wherein all variables are as defined hereinabove.

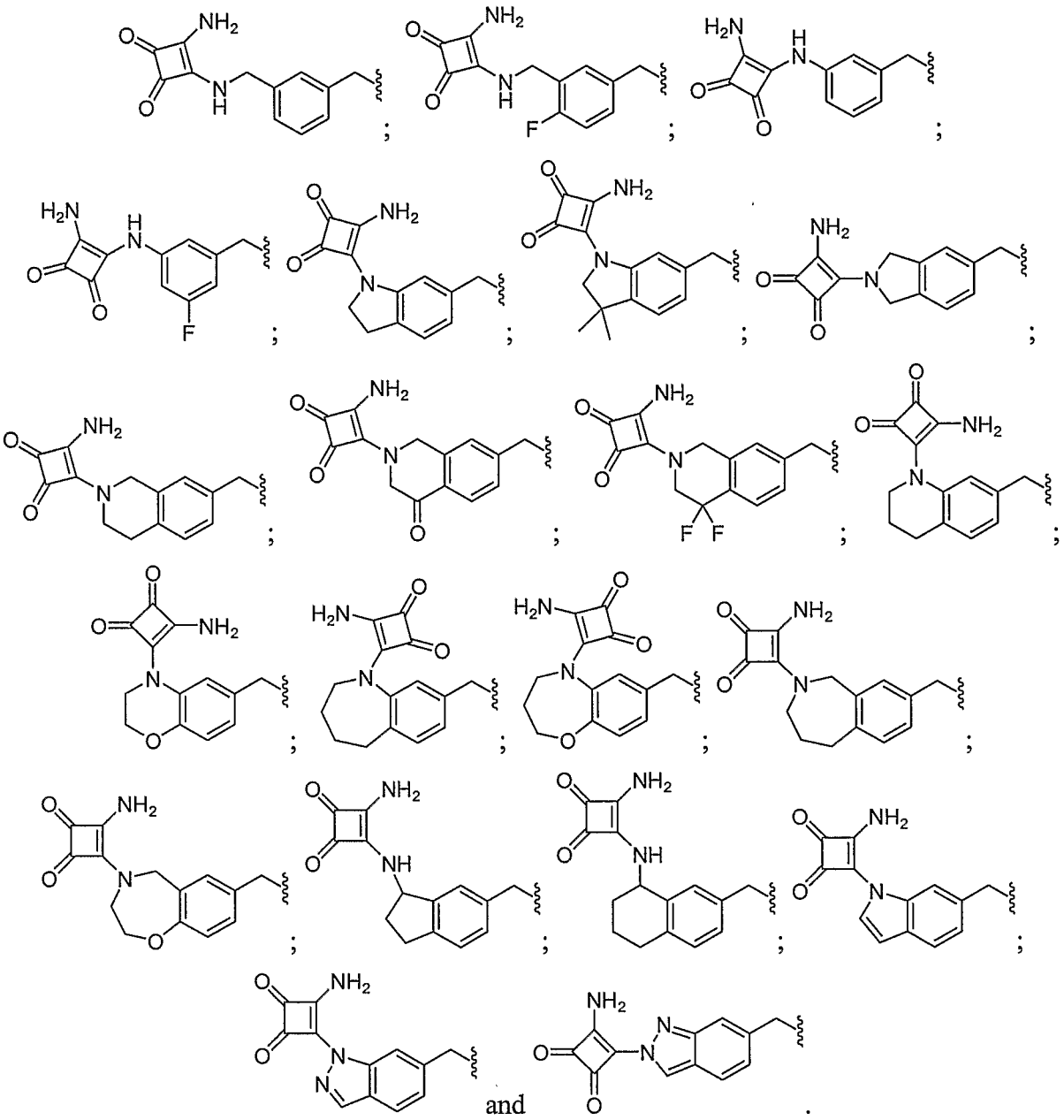
For example, in some embodiments, one R^1 of Group II(a) may be selected from Substituent Group 10 as defined hereinabove.

[0093] In still a further embodiment, one R^1 of Formula (II) may independently be selected from Substituent Group 11:



For example, in some embodiments, one R^1 of Group II(a) may be selected from Substituent Group 11 as defined hereinabove.

[0094] In one embodiment, one R^1 of Formula (II) may be selected from Substituent Group 12:

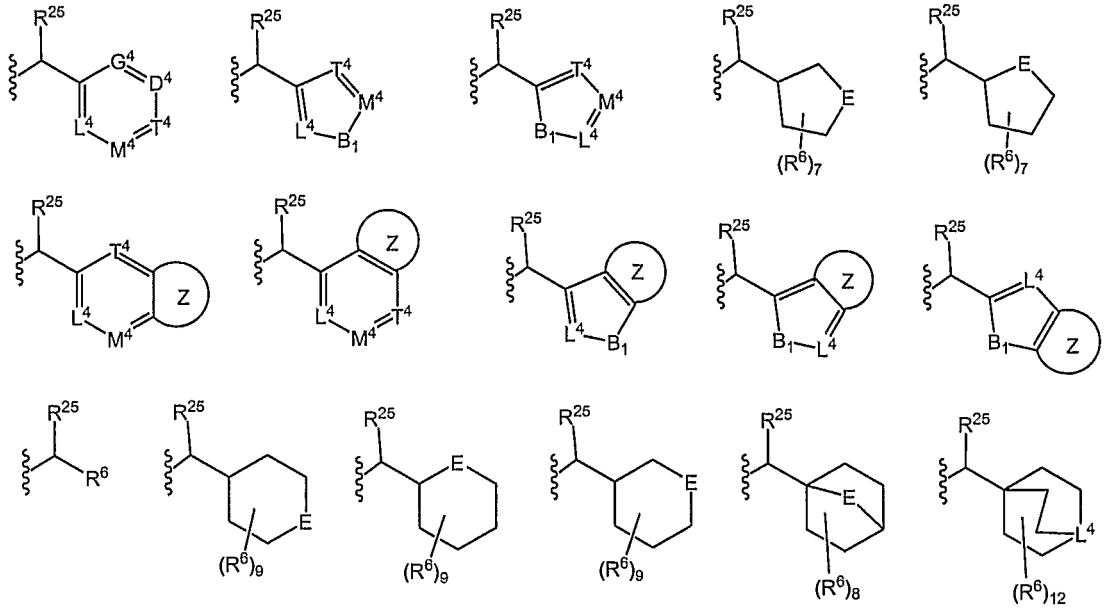


and .

For example, in some embodiments, one R^1 of Group II(a) may be selected from Substituent Group 12 as defined hereinabove.

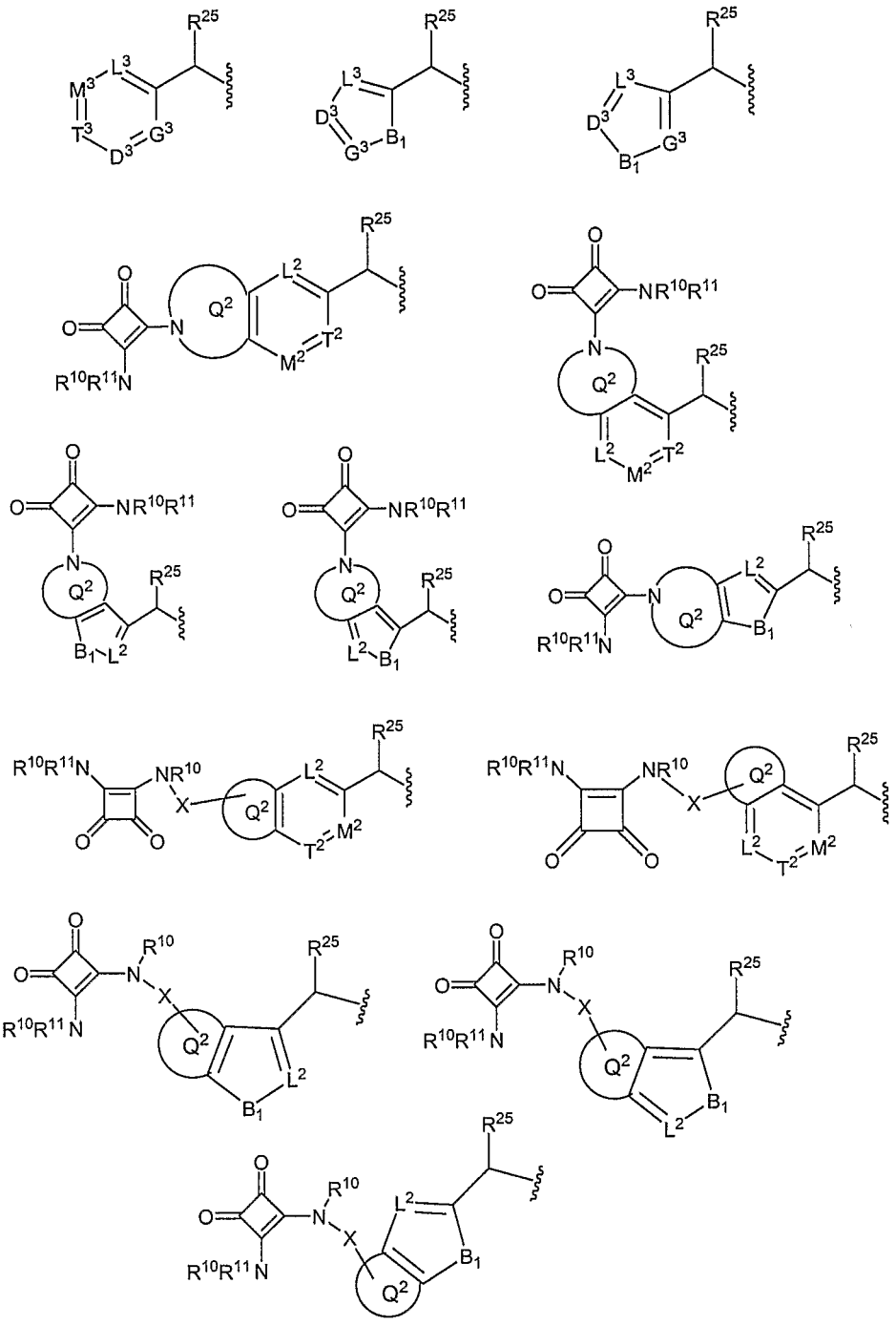
In some embodiments:

A) the first occurrence of R^1 of Formula (II) is selected from Substituent Group 13:



; and

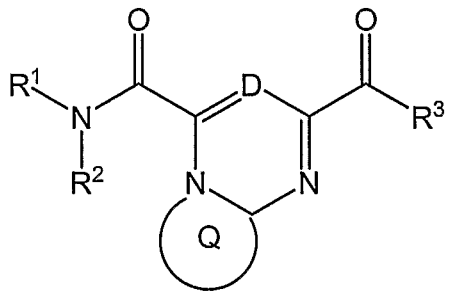
B) the second occurrence R^1 of Formula (II) is selected from Substituent Group 10:



wherein all variables are as defined hereinabove.

For example in some embodiments, the first occurrence of R^1 of the structures of Group II(a) may be selected from Substituent Group 13 as defined hereinabove, and the second occurrence of R^1 may be selected from Substituent Group 10 as defined hereinabove.

[0095] In another embodiment of the present invention, the amide containing heterobicyclic metalloprotease compounds may be represented by the general Formula (III):

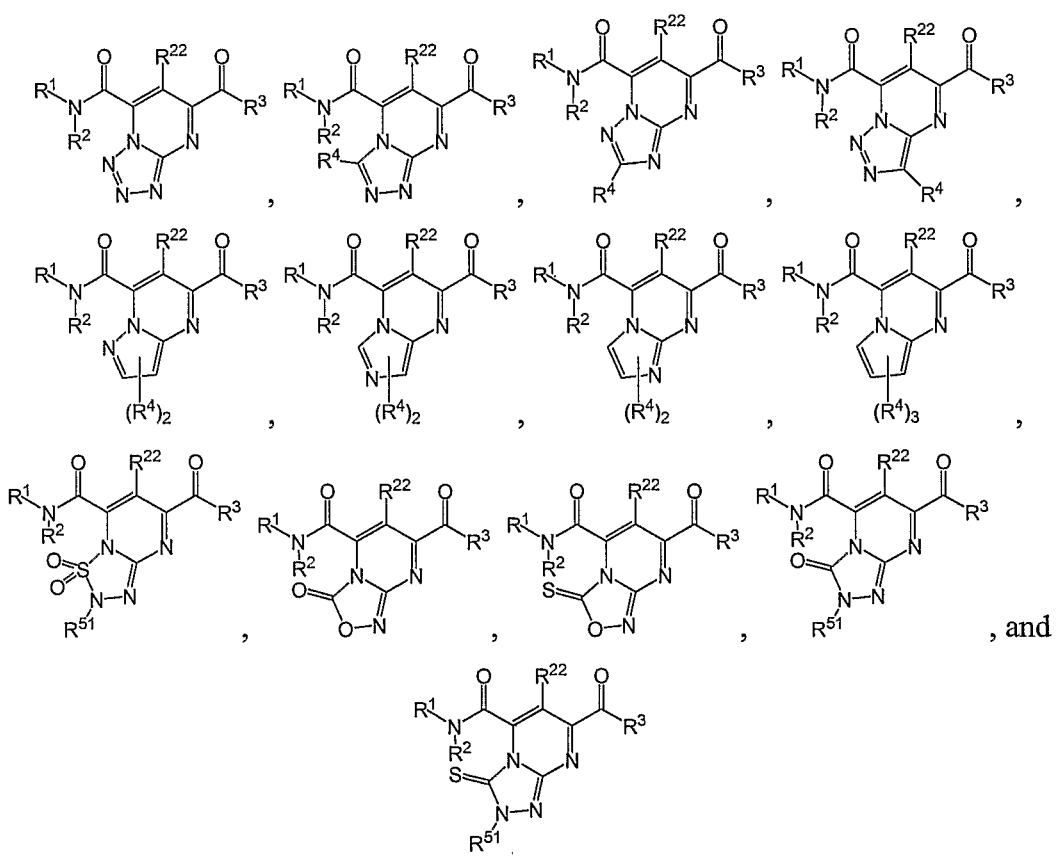


Formula (III)

and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof,

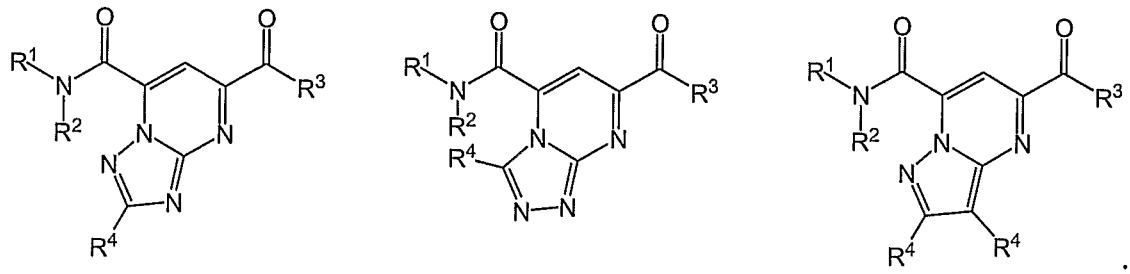
wherein all variables are as defined hereinabove.

[0096] In yet another embodiment, the compounds of Formula (III) may be selected from Group III(a):

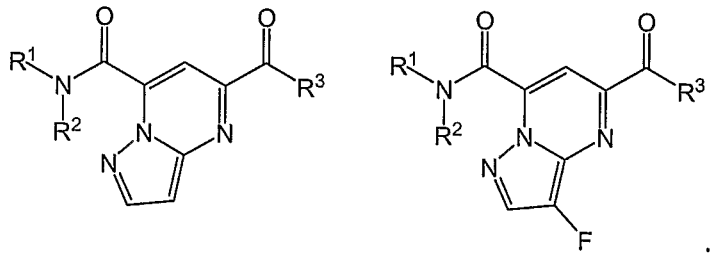


wherein all variables are as defined hereinabove.

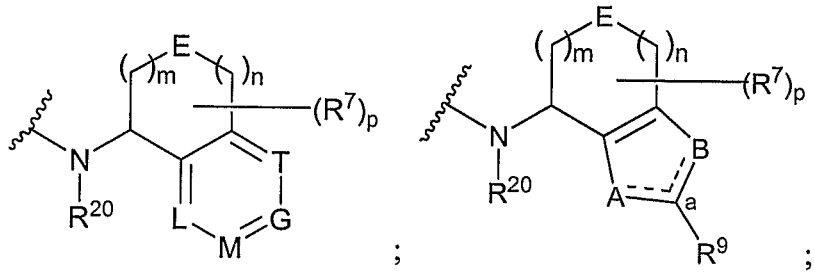
[0097] In still another embodiment, the compounds of Formula (III) may be selected from:

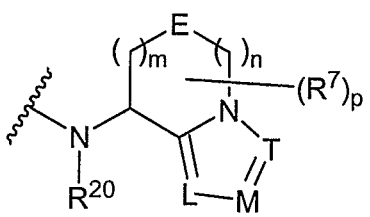


[0098] In a further embodiment, the compounds of Formula (III) may be selected from:



[0099] In yet a further embodiment, R^3 of Formula (III) may be selected from Substituent Group 1:

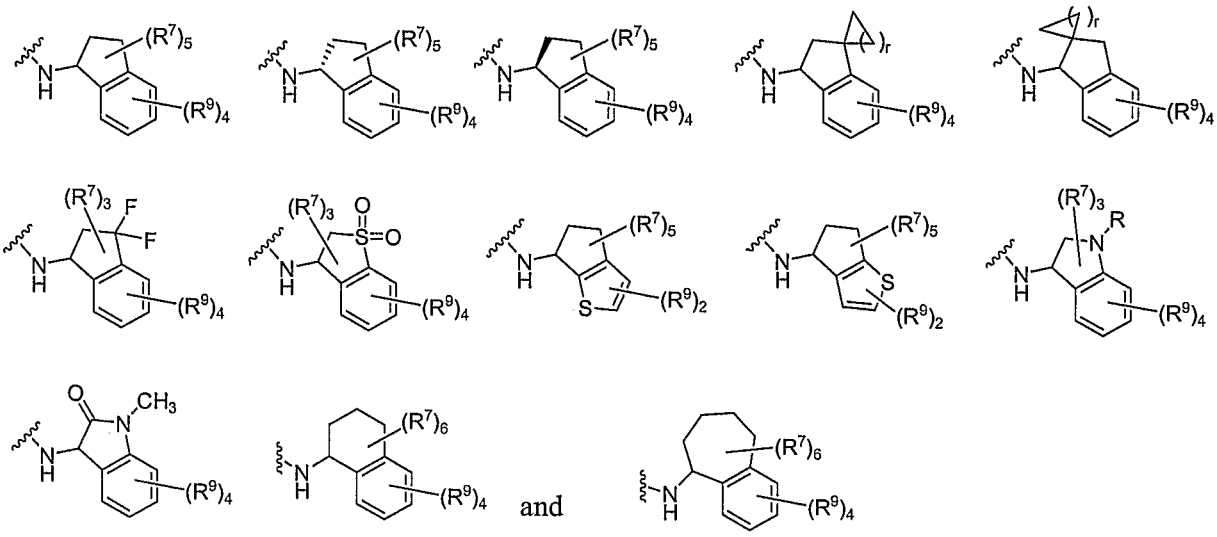

; ; and



wherein all variables are as defined hereinabove.

For example, in some embodiments, R^3 of the structures of Group III(a) may be selected from Substituent Group 1 as defined hereinabove.

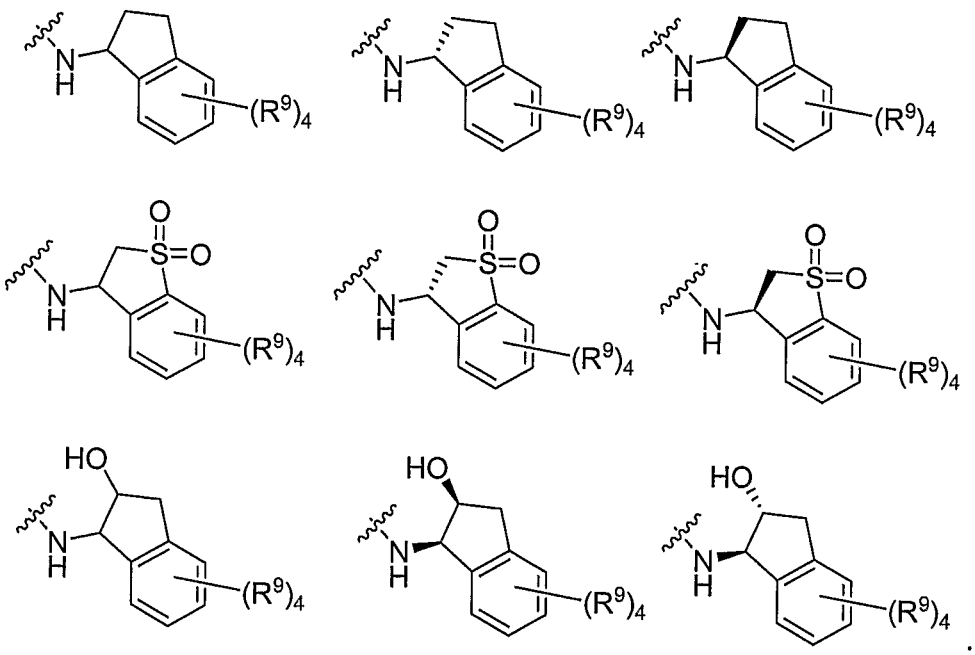
[0100] In still a further embodiment, R^3 of Formula (III) may be selected from Substituent Group 2:


and

wherein all variables are as defined hereinabove.

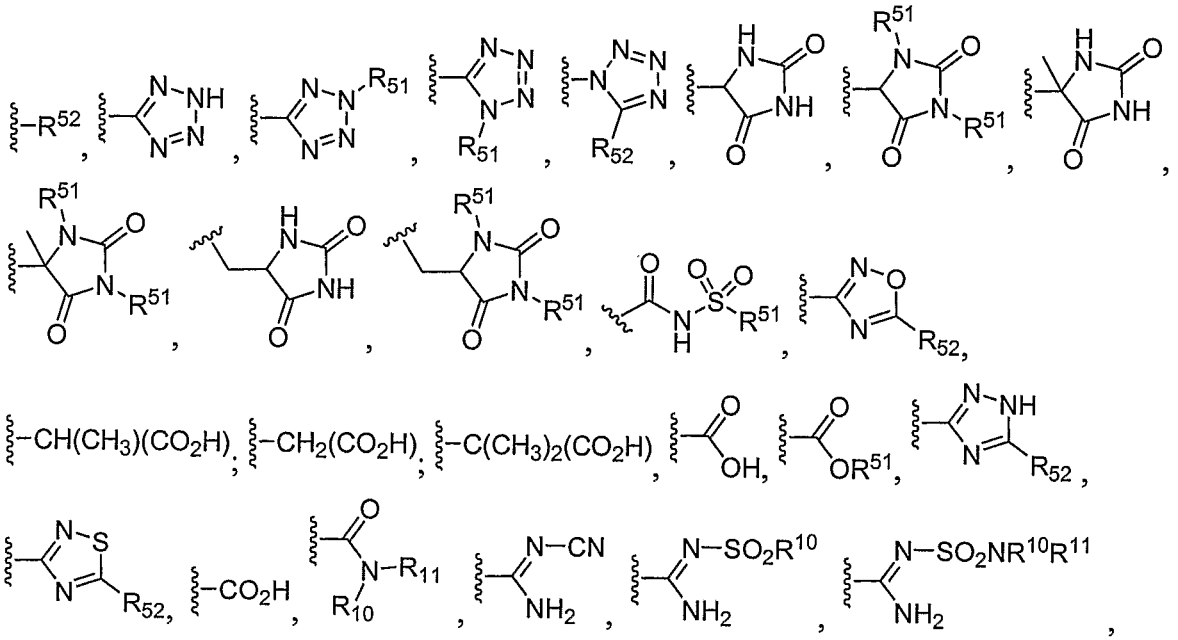
[0101] In still a further embodiment, R^3 of the structures of Group III(a) may be selected from Substituent Group 2 as defined hereinabove.

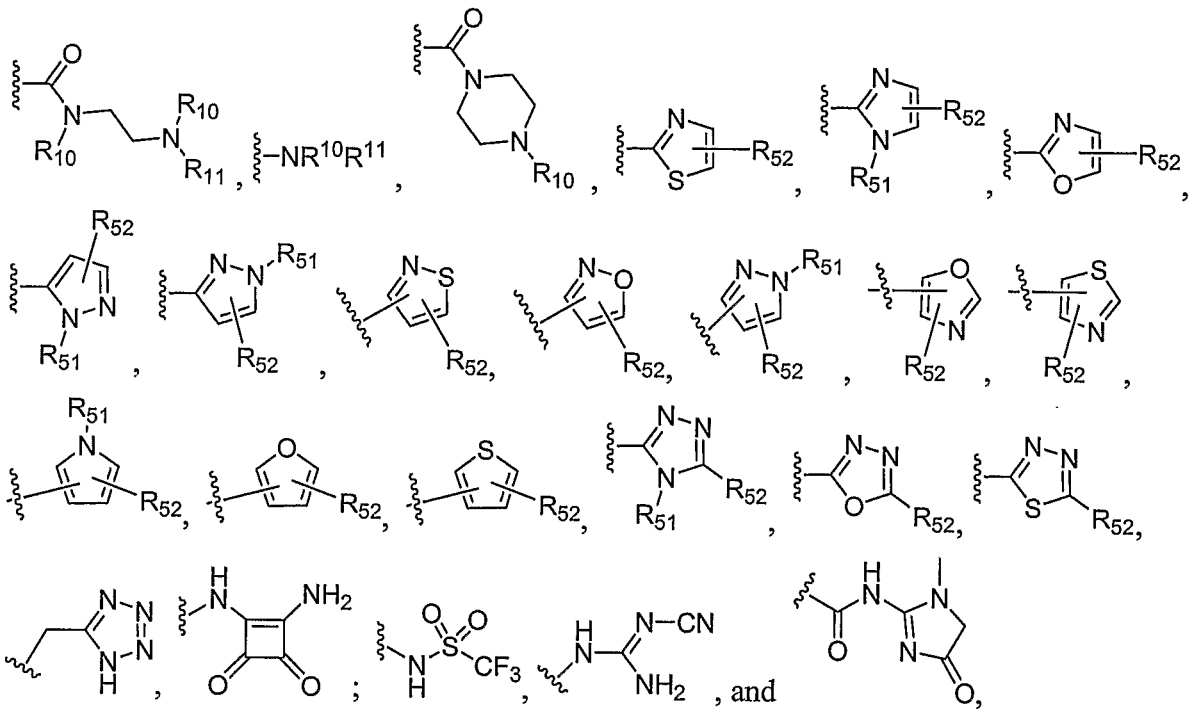
[0102] In one embodiment, R^3 of Formula (III) may be selected from Substituent Group 3:



[0103] For example, in some embodiments, R^3 of the structures of Group III(a) may be selected from Substituent Group 3 as defined hereinabove.

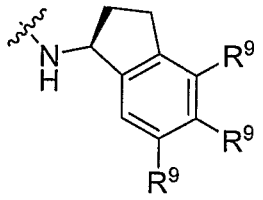
[0104] In one embodiment, R^9 of the structures of Substituent Group 3 may be selected from:





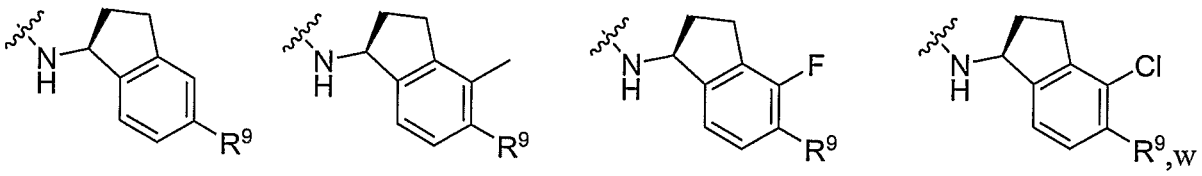
wherein all variables are as defined hereinabove.

[0100] In another embodiment, R^3 of Formula (III) may be Substituent Group 16:

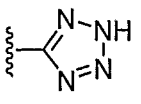
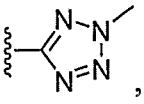
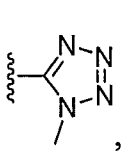
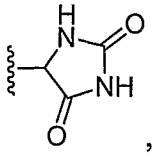
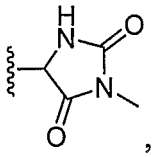
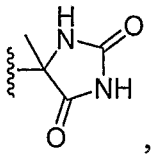
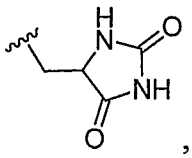
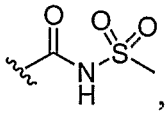
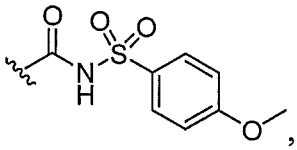
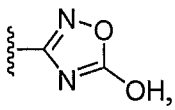
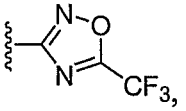
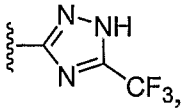
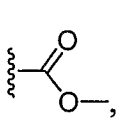
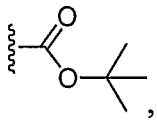
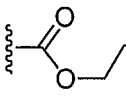
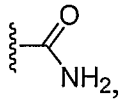
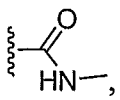
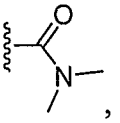
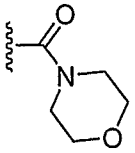


For example, in some embodiments, R^3 of the structures of Group III(a) may be Substituent Group 16 as defined hereinabove.

[0101] In yet another embodiment, R^3 of Formula (III) may be selected from Substituent Group 5:

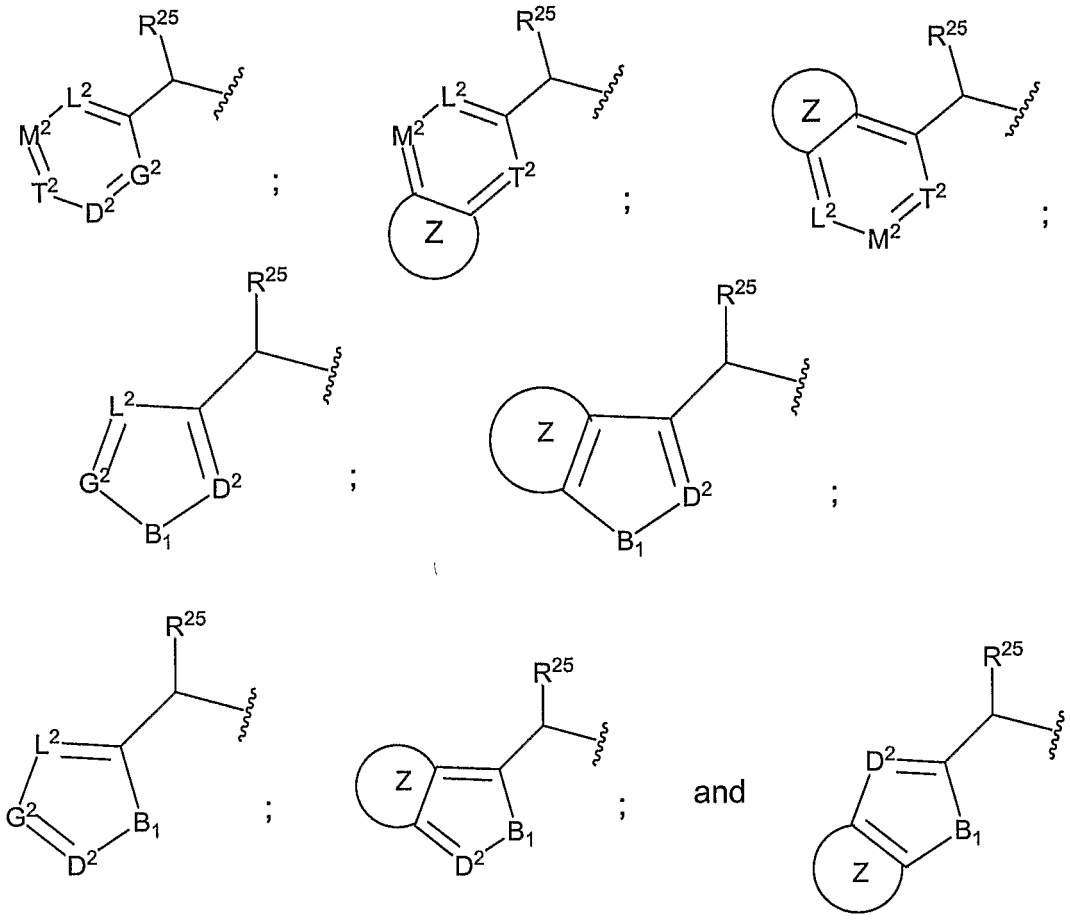


herein:

R^9 is selected from hydrogen, fluoro, halo, CN, alkyl, CO_2H,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

For example, in some embodiments, R^3 of the structures of Group III(a) may be selected from Substituent Group 5 as defined hereinabove.

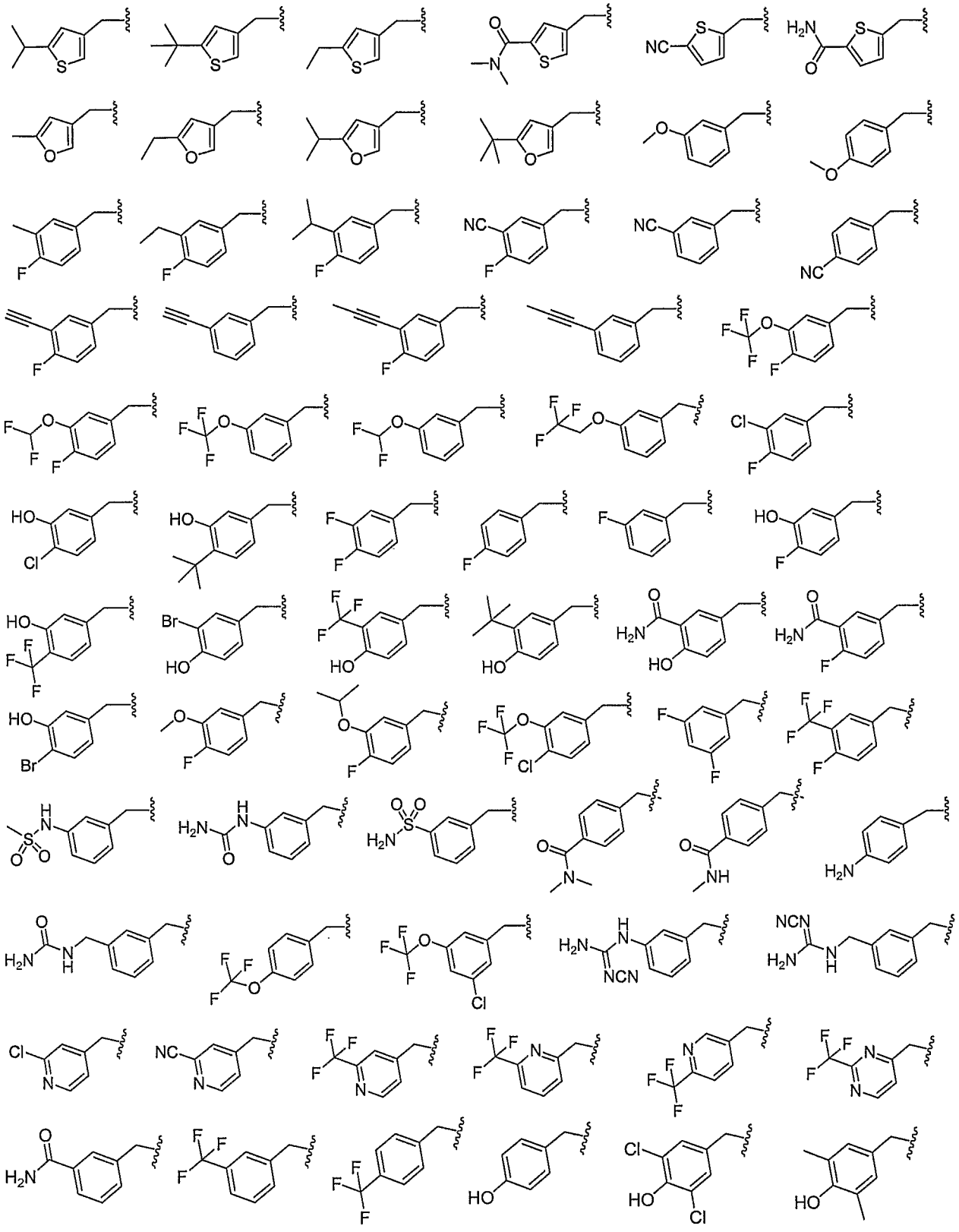
[0102] In still another embodiment, R^1 of the structures of Formula (III) may be selected from Substituent Group 6:



wherein all variables are as defined hereinabove.

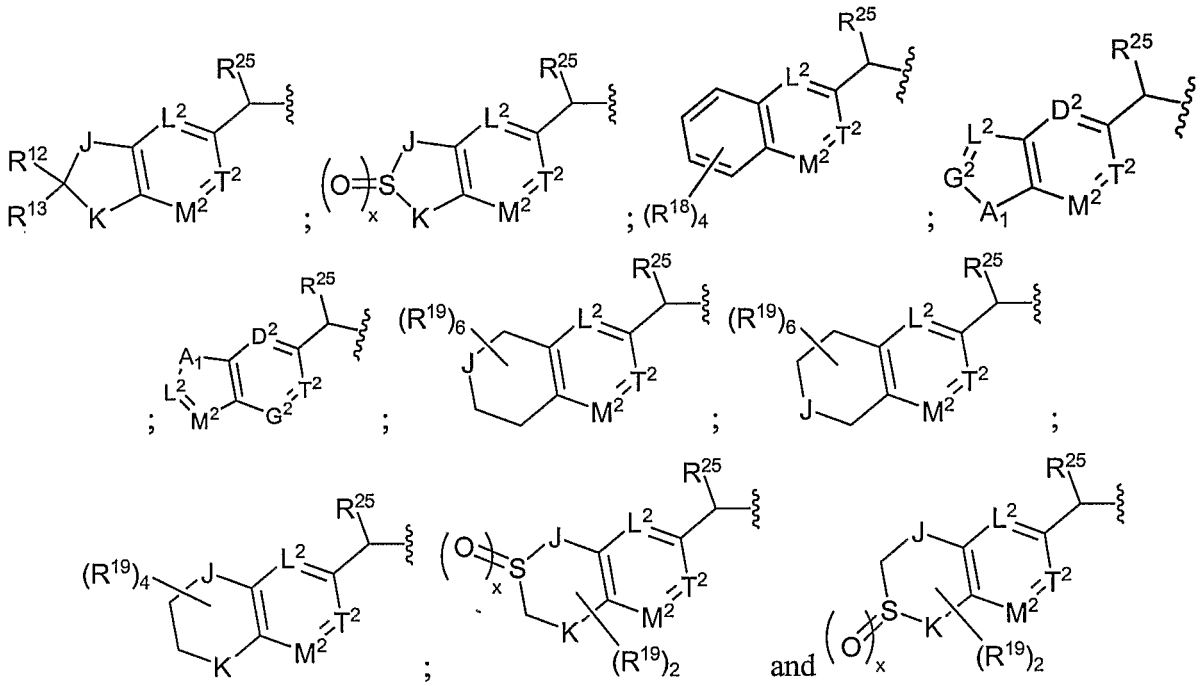
For example, in some embodiments, R^1 of the structures of Group III(a) may be selected from Substituent Group 6 as defined hereinabove.

[0103] In a further embodiment, R^1 of Formula (III) may be selected from Substituent Group 7:



[0104] For example, in some embodiments, R^1 of the structures of Group III(a) may be selected from Substituent Group 7 as defined hereinabove.

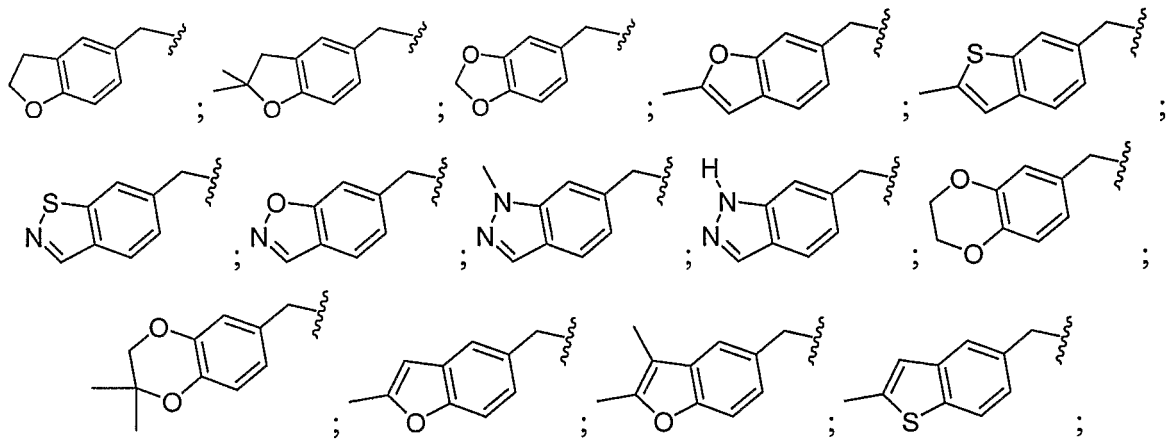
[0105] In yet a further embodiment, R^1 of Formula (III) may be selected from Substituent Group 8:

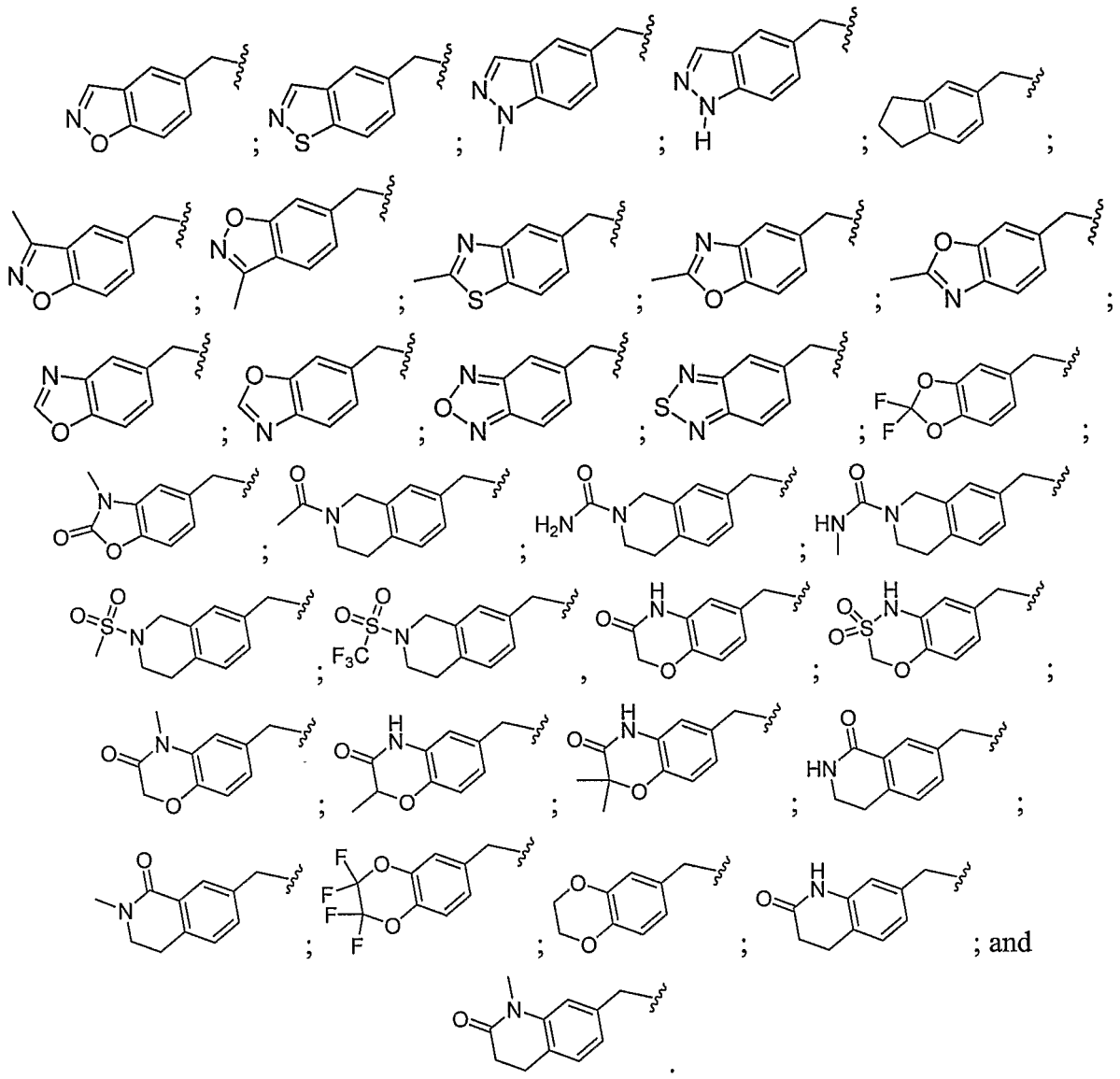


wherein all variables are as defined hereinabove.

For example, in some embodiments, R^1 of the structures of Group III(a) may be selected from Substituent Group 8 as defined hereinabove.

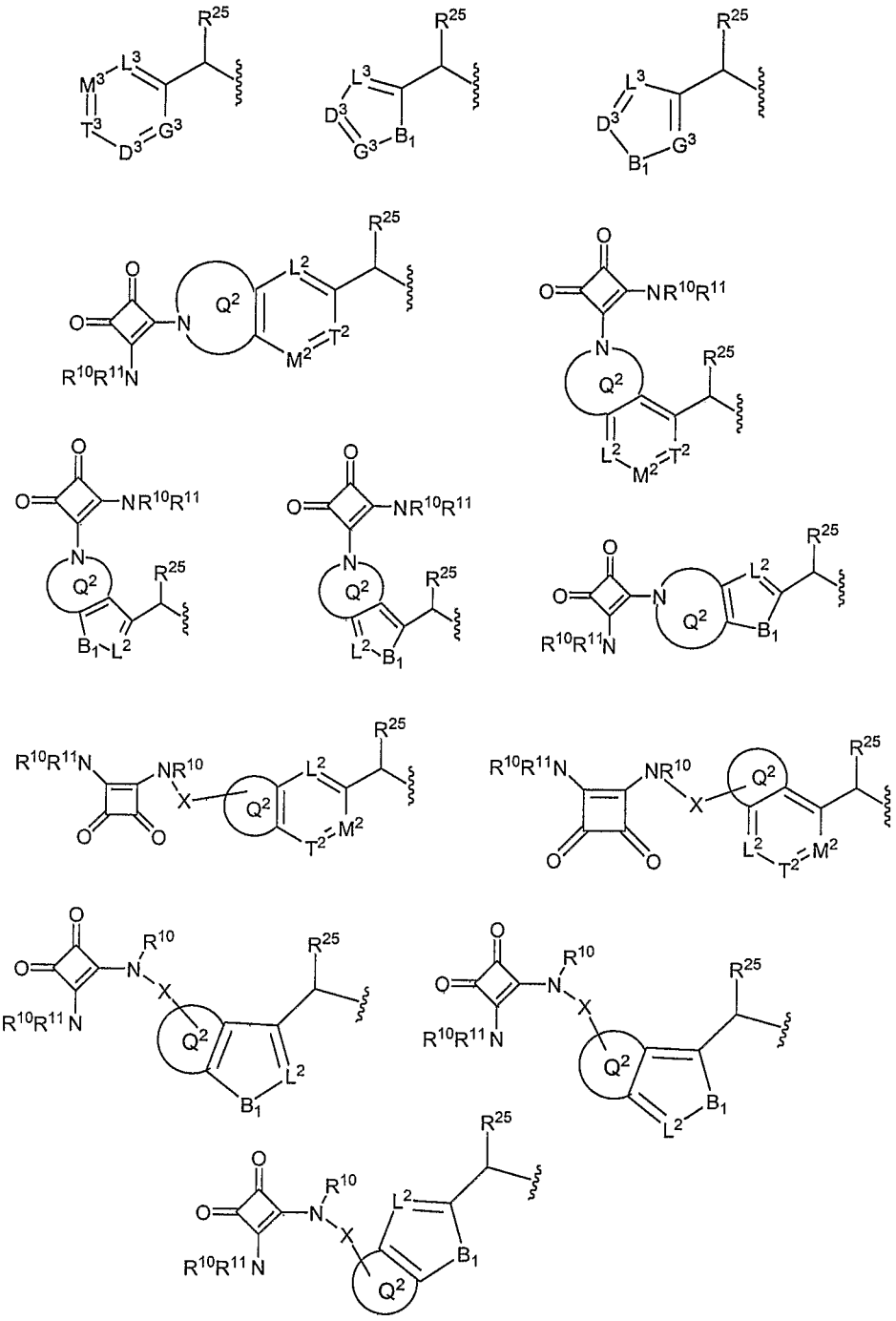
[0106] In still a further embodiment, R^1 of Formula (III) may be selected from Substituent Group 9:





For example, in some embodiments, R^1 of the structures of Group III(a) may be selected from Substituent Group 9 as defined hereinabove.

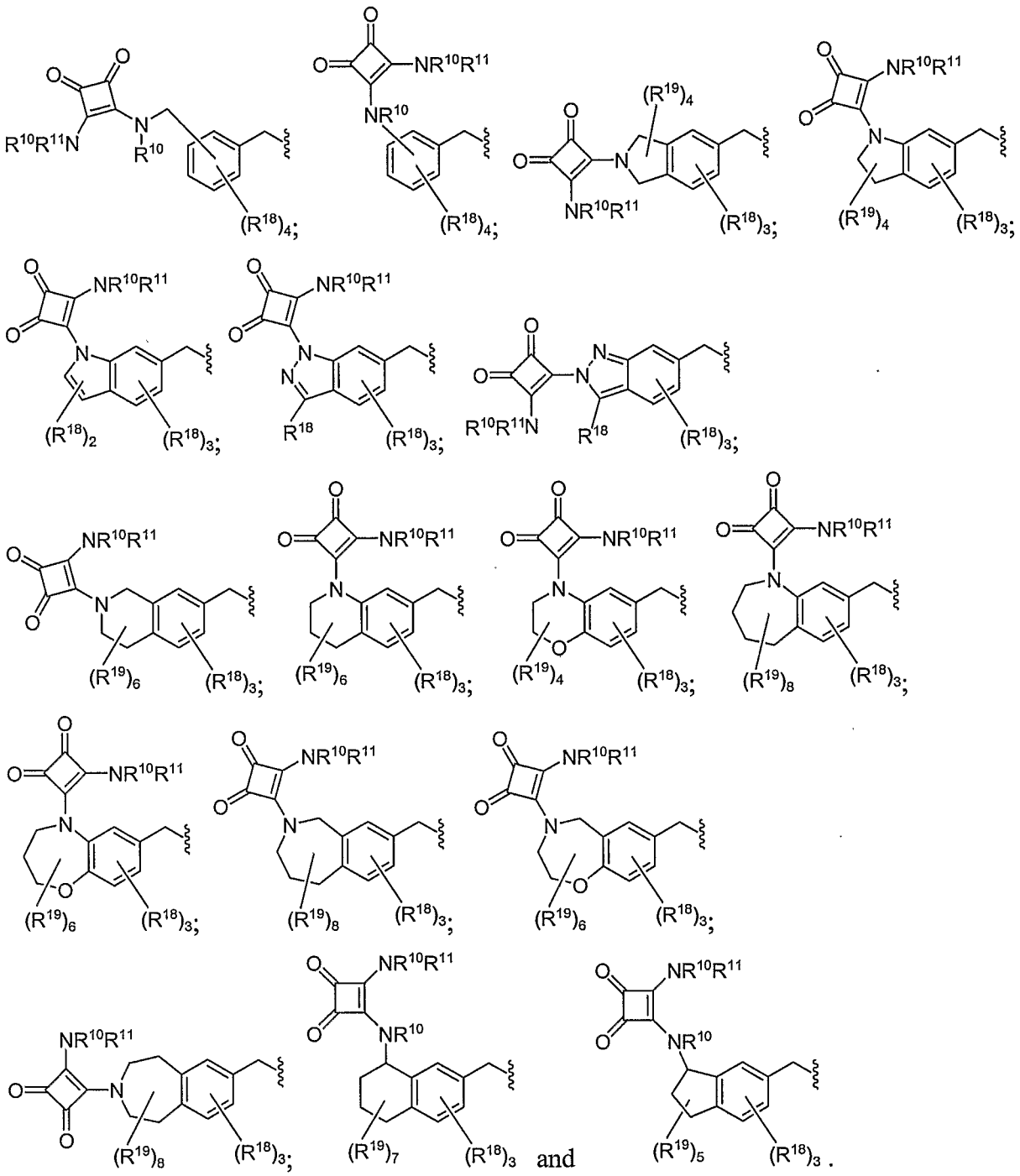
[0107] In one embodiment, R^1 of Group III(a) may be selected from Substituent Group 10.



wherein all variables are as defined hereinabove.

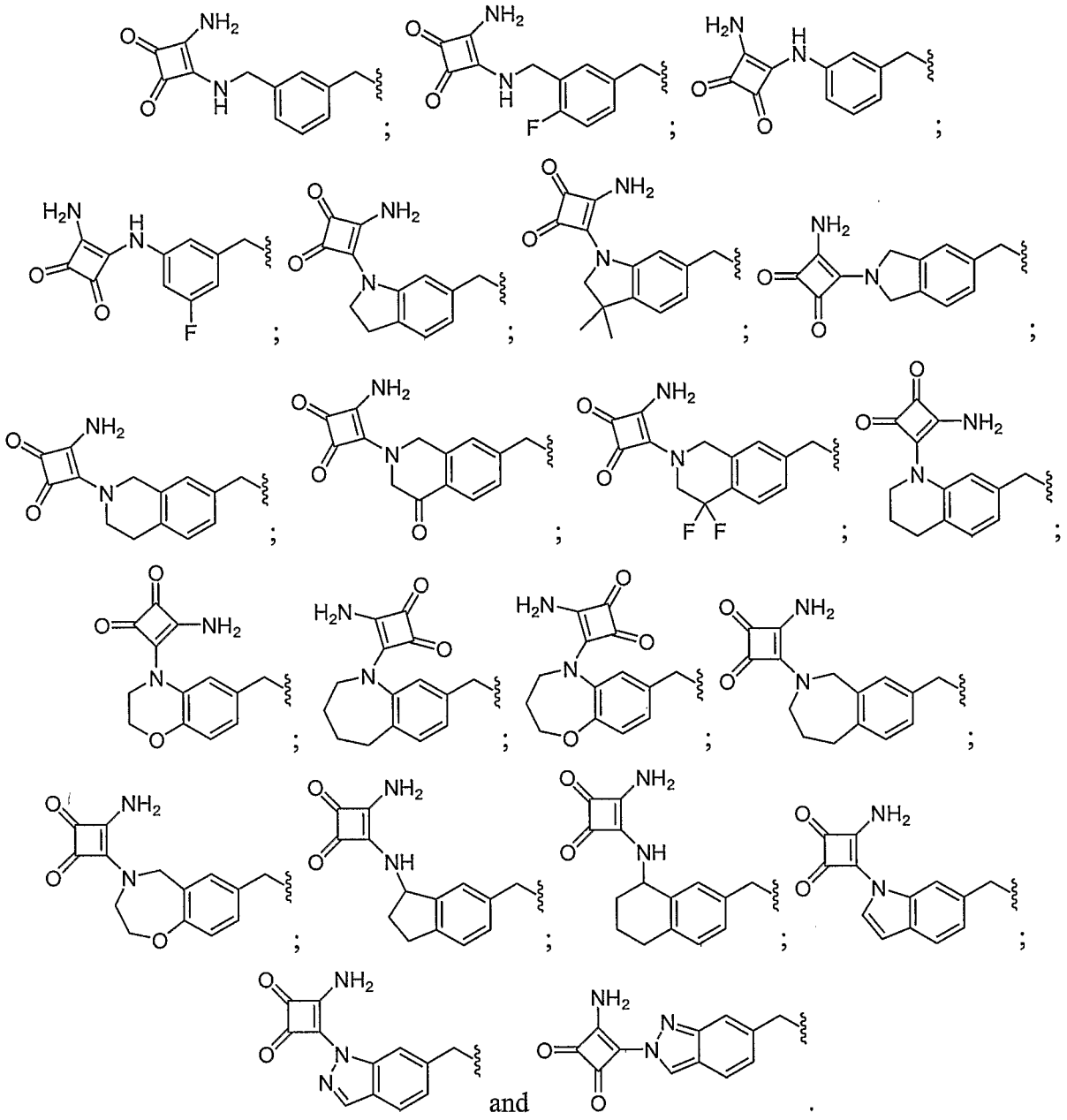
For example, in some embodiments, R^1 of the structures of Group III(a) may be selected from Substituent Group 10 as defined hereinabove.

[0108] In another embodiment, R^1 of Formula (III) may be selected from Substituent Group 11:



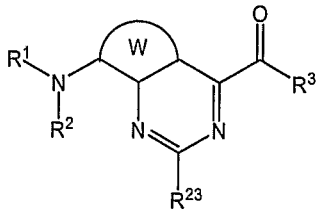
[0109] For example, in some embodiments, R^1 of the structures of Group III(a) may be selected from Substituent Group 11 as defined hereinabove.

[0110] In yet another embodiment, R^1 of Formula (III) may be selected from Substituent Group 12:



For example, in some embodiments, R^1 of the structures of Group III(a) may be selected from Substituent Group 12 as defined hereinabove.

[0111] In one embodiment of the present invention, the amide containing heterobicyclic metalloprotease compounds may be represented by the general Formula (IV):



Formula (IV)

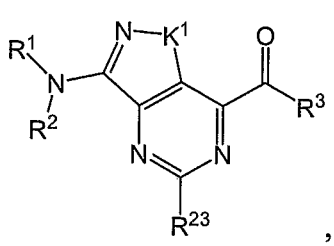
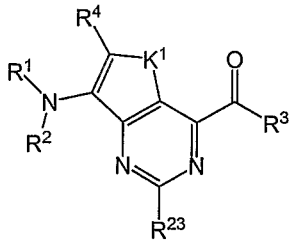
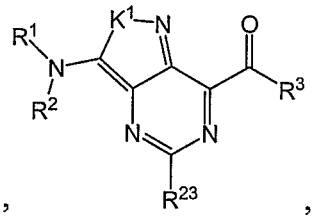
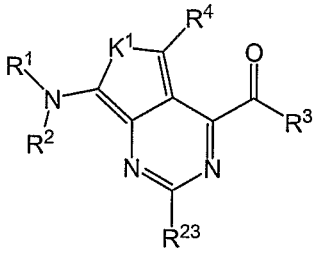
and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof,

wherein

W is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4; and

all remaining variables are as defined herein above.

[0112] In another embodiment, the compounds of Formula (IV) may be selected from Group IV(a):

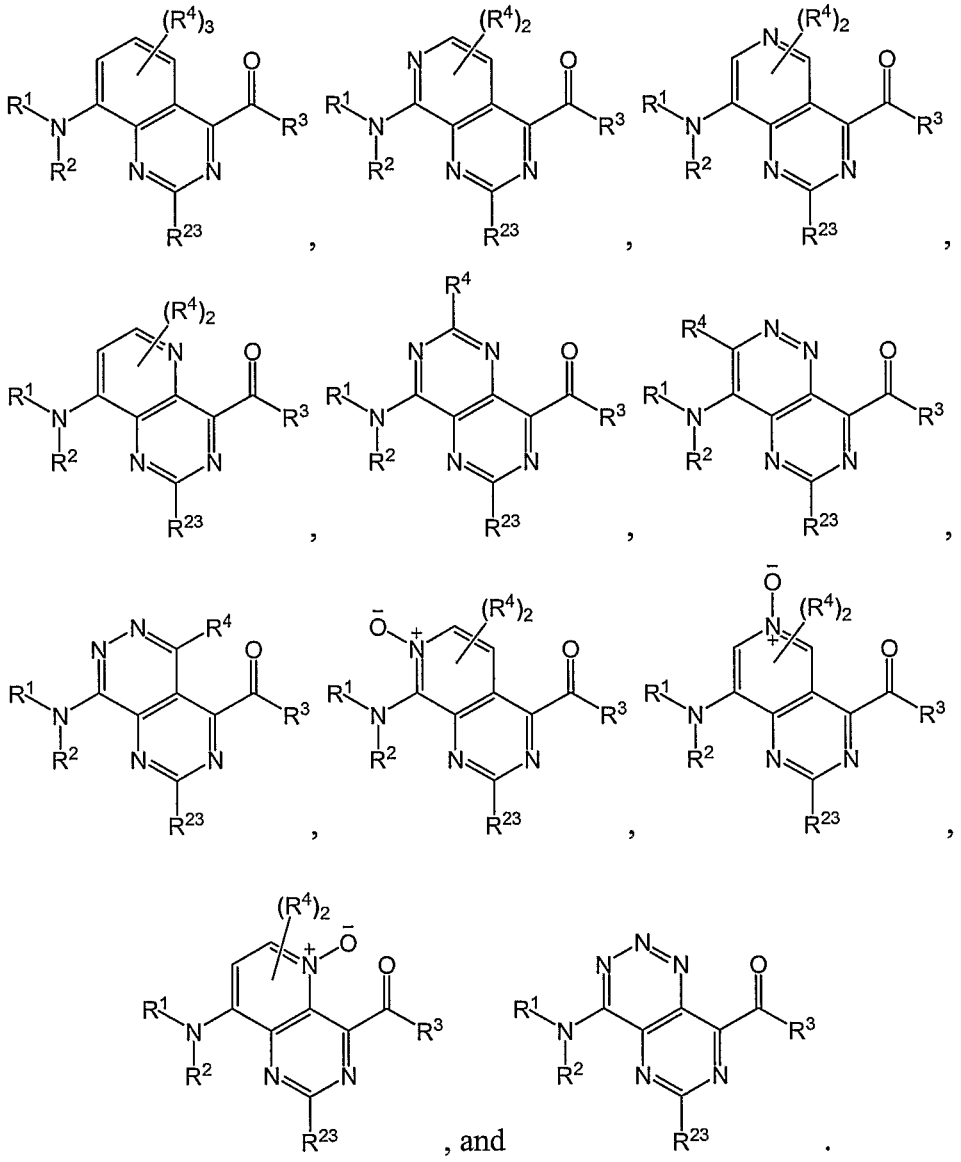

,

,

, and


wherein:

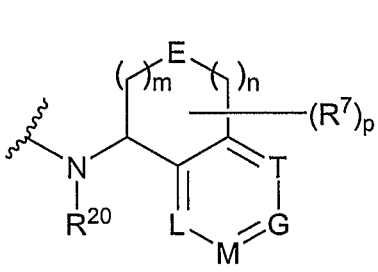
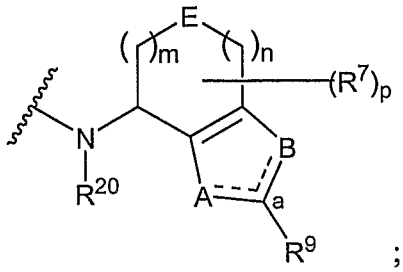
K^1 is O, S, or NR^{51}; and

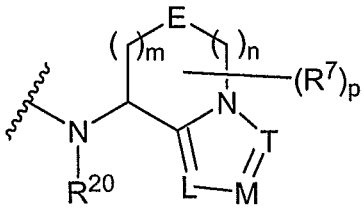
all remaining variables are as defined hereinabove.

[0113] In yet another embodiment, the compounds of Formula (IV) may be selected from Group IV(b):



[0114] In still another embodiment, R^3 of Formula (IV) may be selected from Substituent Group 1:

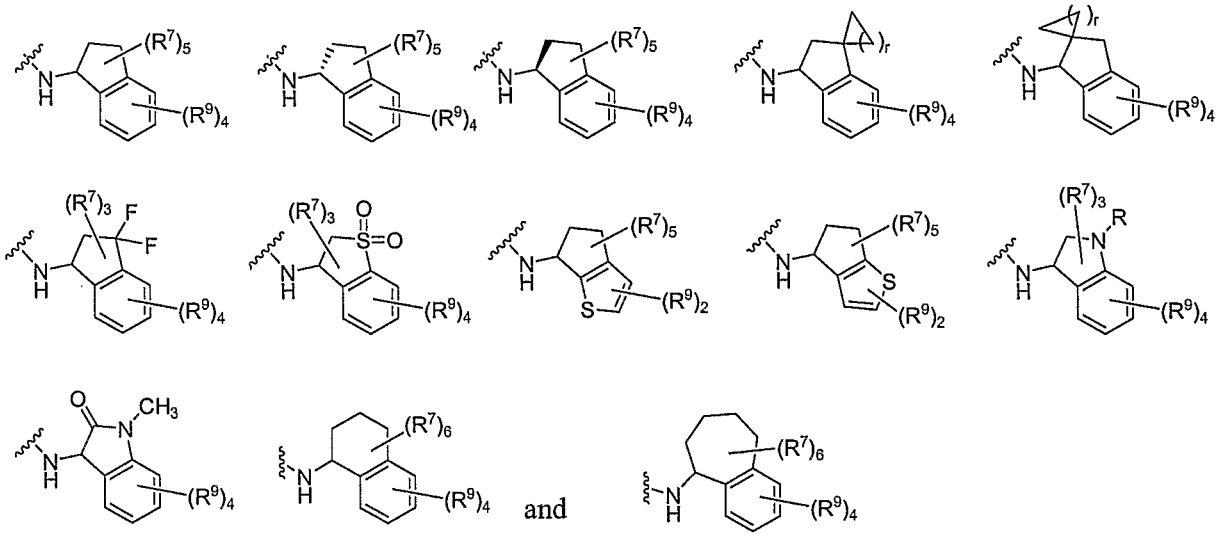


; ; and



wherein all variables are as defined hereinabove.

For example, in some embodiments, R^3 of the structures of Groups IV(a) and (b) may be selected from Substituent Group 1 as defined hereinabove.

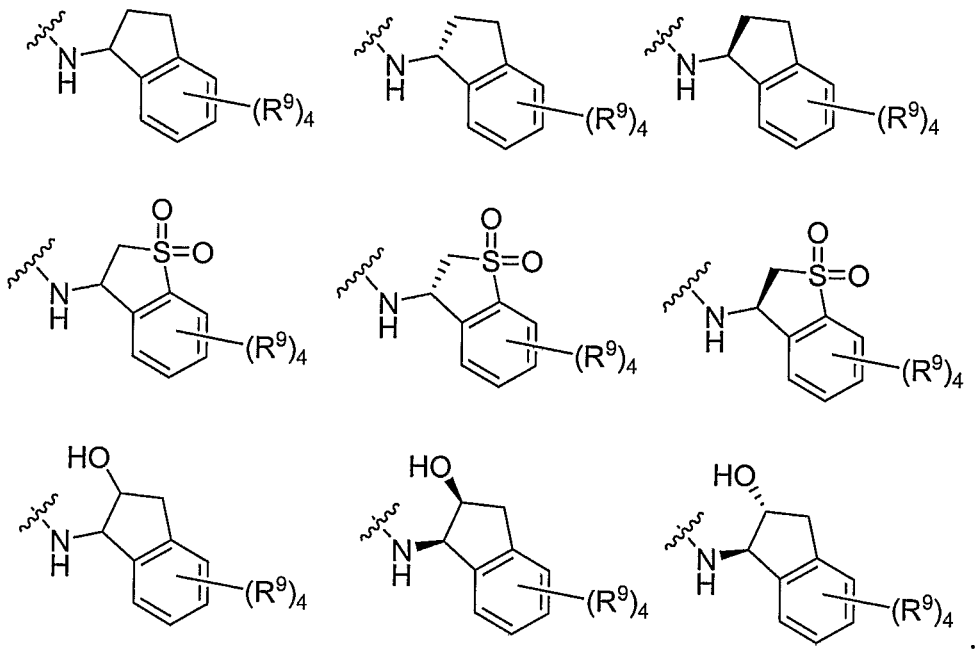
[0115] In a further embodiment, R^3 of Formula (IV) may be selected from Substituent Group 2:


and

wherein all variables are as defined hereinabove

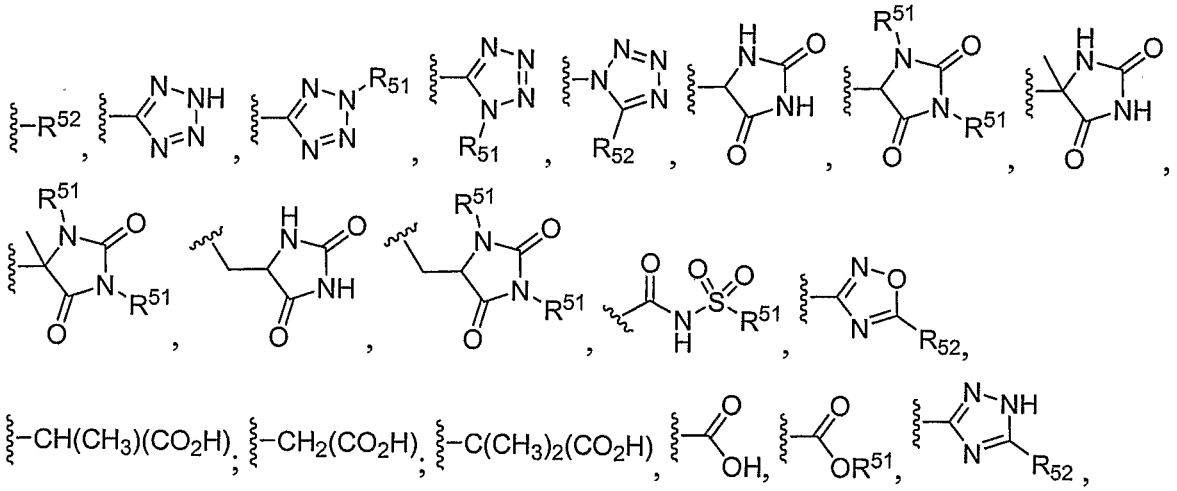
For example, in some embodiments, R^3 of the structures of Groups IV(a) and (b) may be selected from Substituent Group 2 as defined hereinabove.

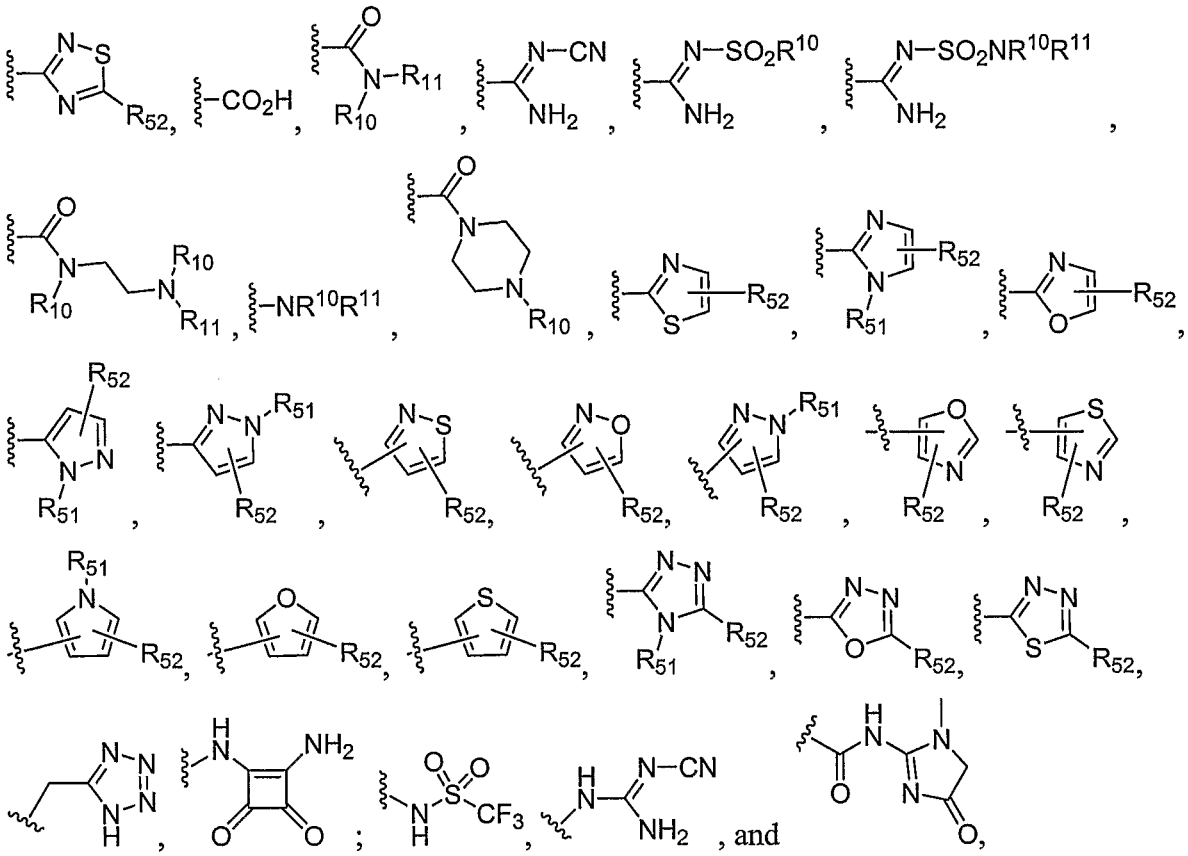
[0116] In yet a further embodiment, R^3 of Formula (IV) may be selected from Substituent Group 3



For example, in some embodiments, R^3 of the structures of Groups IV(a) and (b) may be selected from Substituent Group 3 as defined hereinabove.

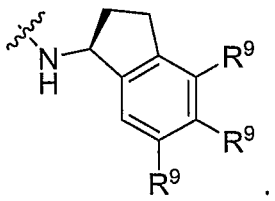
[0117] In still a further embodiment, R^9 of Substituent Group 3 may be selected from:





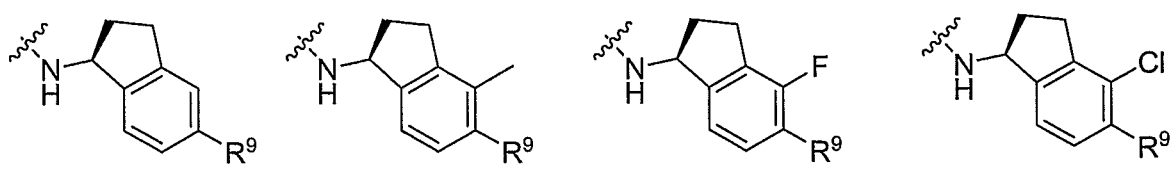
wherein all variables are as defined hereinabove.

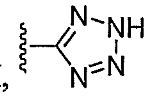
[0118] In one embodiment, R^3 of Formula (IV) may be Substituent Group 16:

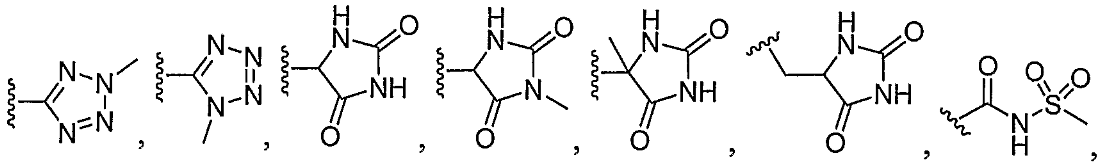


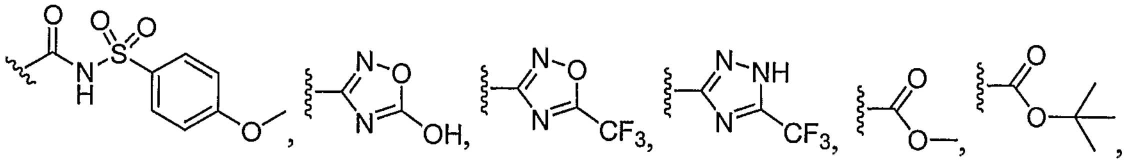
For example, in some embodiments, R^3 of the structures of Groups IV(a) and (b) may be Substituent Group 16 as defined hereinabove.

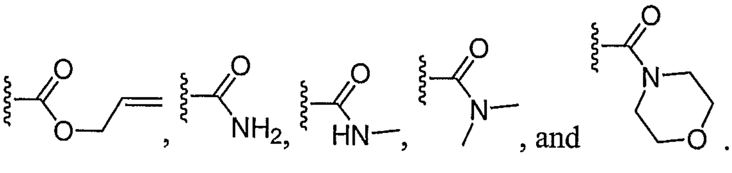
[0119] In another embodiment, R^3 of Formula (IV) may be selected from Substituent Group 5:



wherein R^9 is selected from hydrogen, fluoro, halo, CN, alkyl, CO_2H,  ,

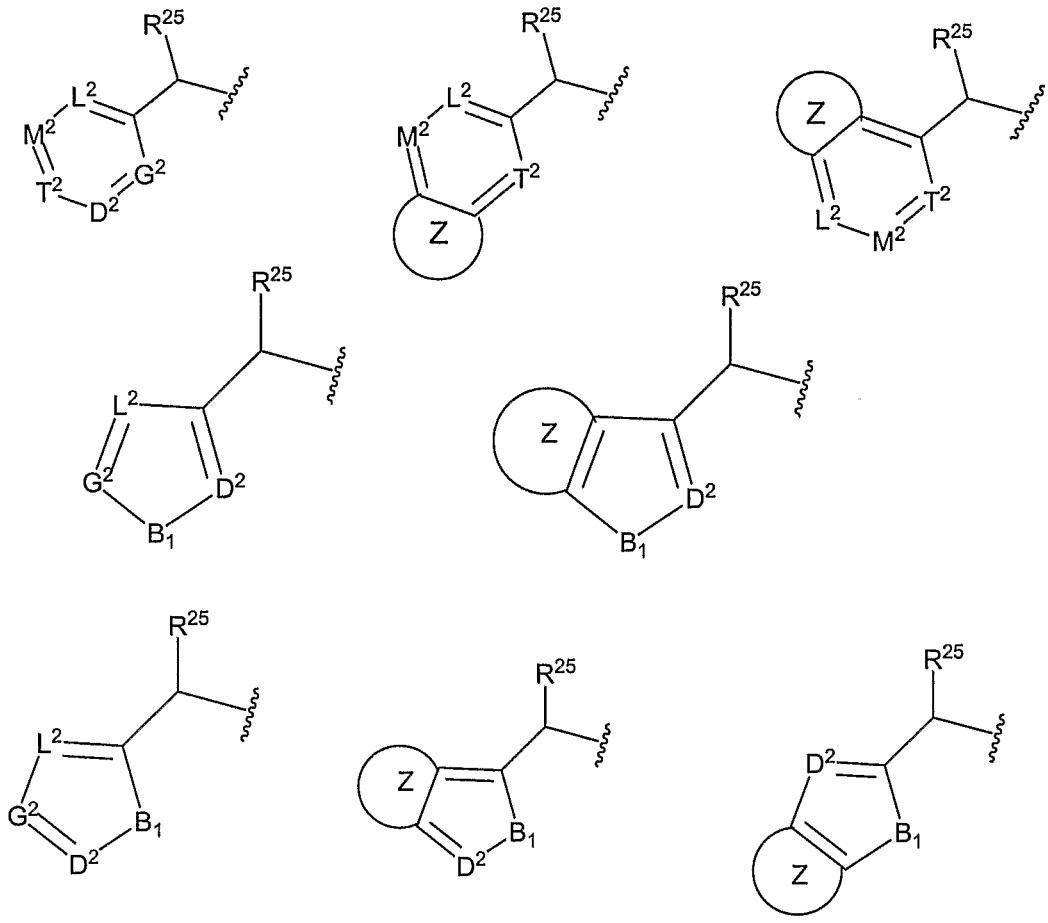






For example, in some embodiments, R^3 of the structures of Groups IV(a) and (b) may be selected from Substituent Group 5 as defined hereinabove.

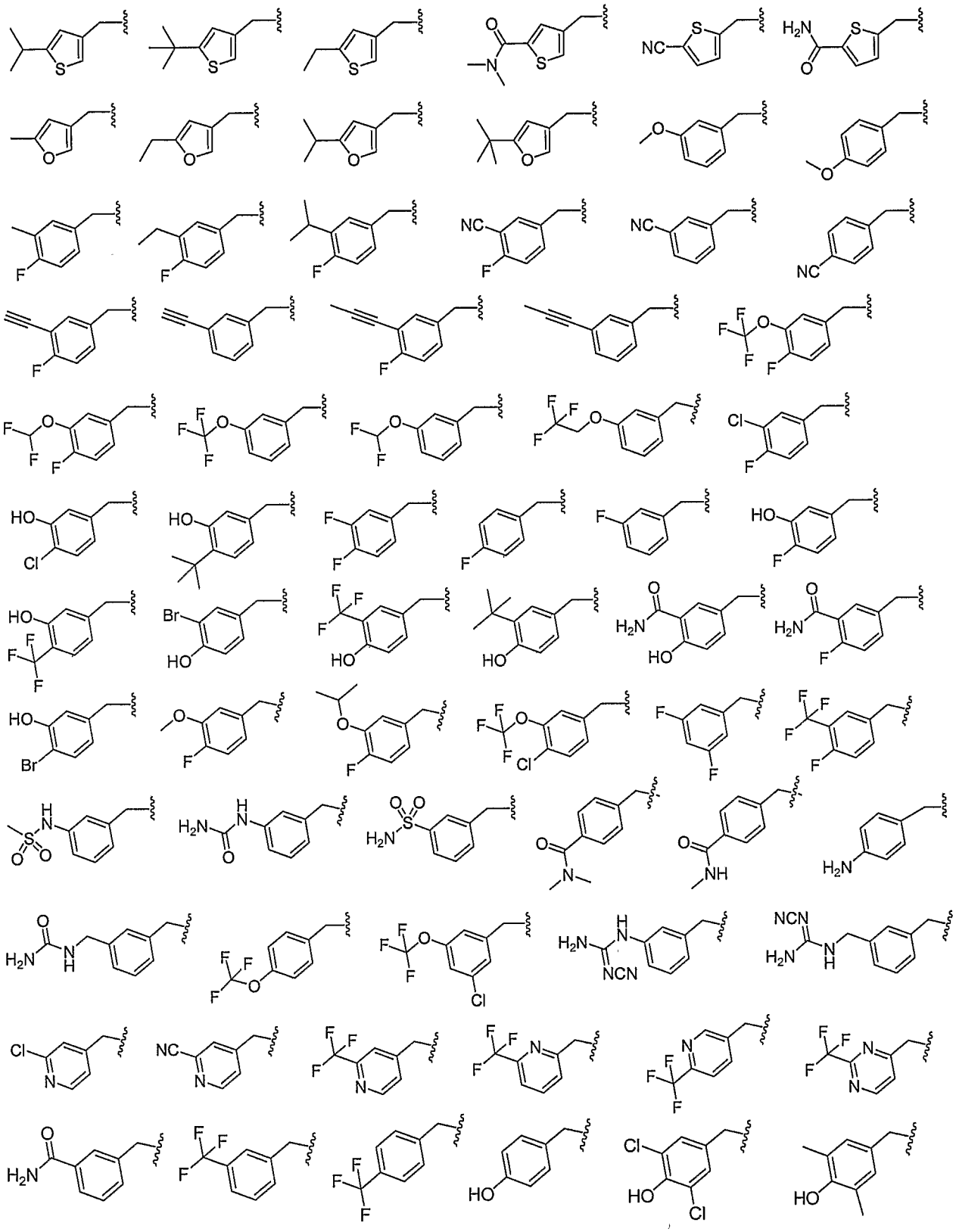
[0120] In yet another embodiment, R^1 of Formula (IV) may be selected from Substituent Group 6:



wherein all variables are as defined hereinabove.

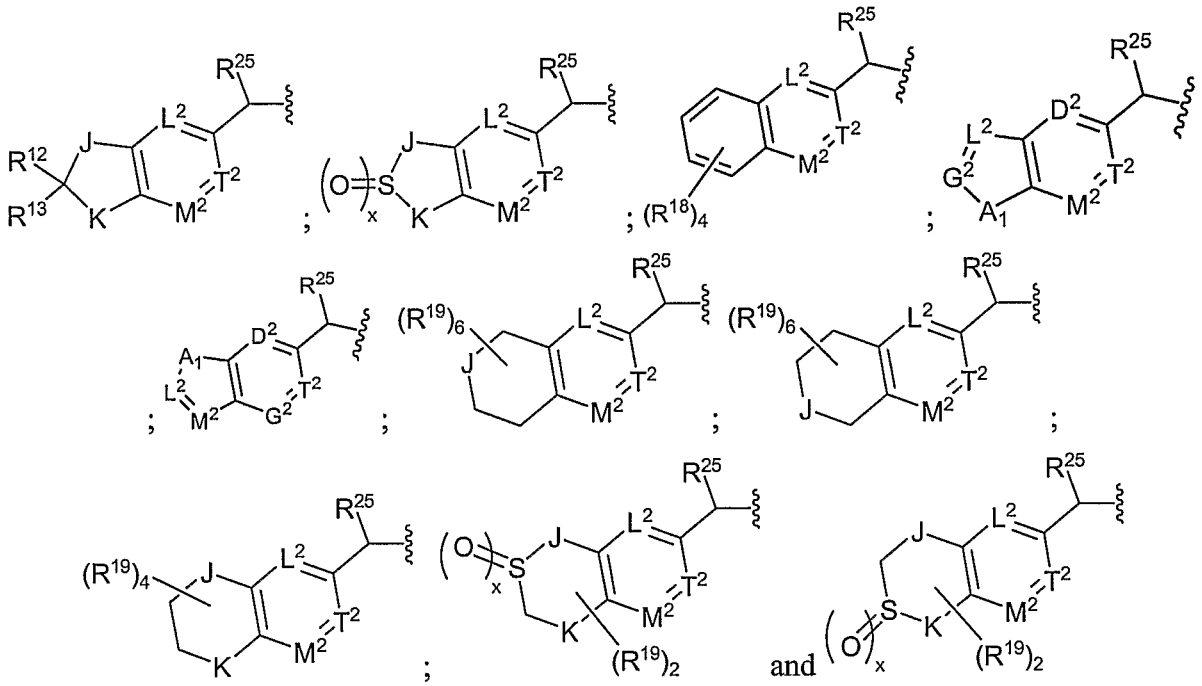
For example, in some embodiments, R^1 of the structures of Groups IV(a) and (b) may be selected from Substituent Group 6 as defined hereinabove.

[0121] In still another embodiment, R^1 of Formula (IV) may be selected from Substituent Group 7:



For example, in some embodiments, R^1 of the structures of Groups IV(a) and (b) may be selected from Substituent Group 7 as defined hereinabove.

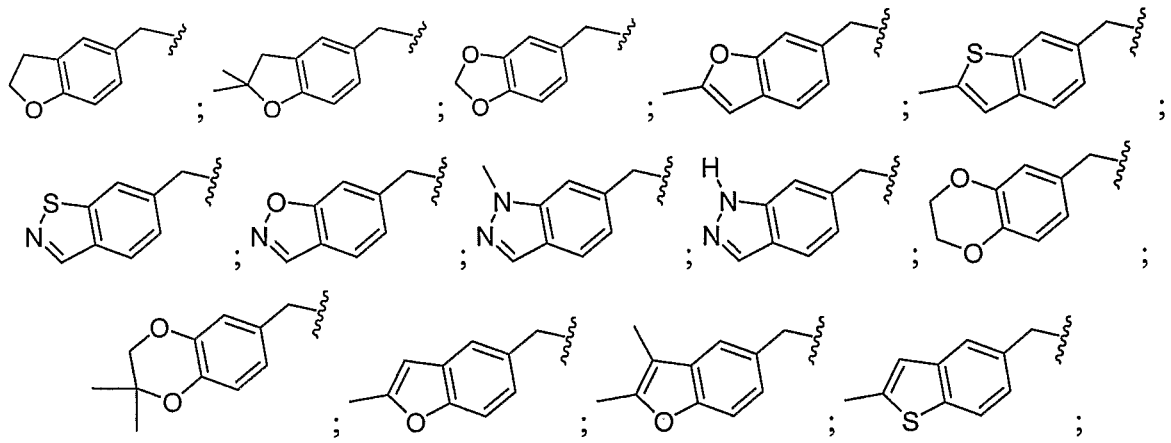
[0122] In a further embodiment, R^1 of Formula (IV) may be selected from Substituent Group 8:

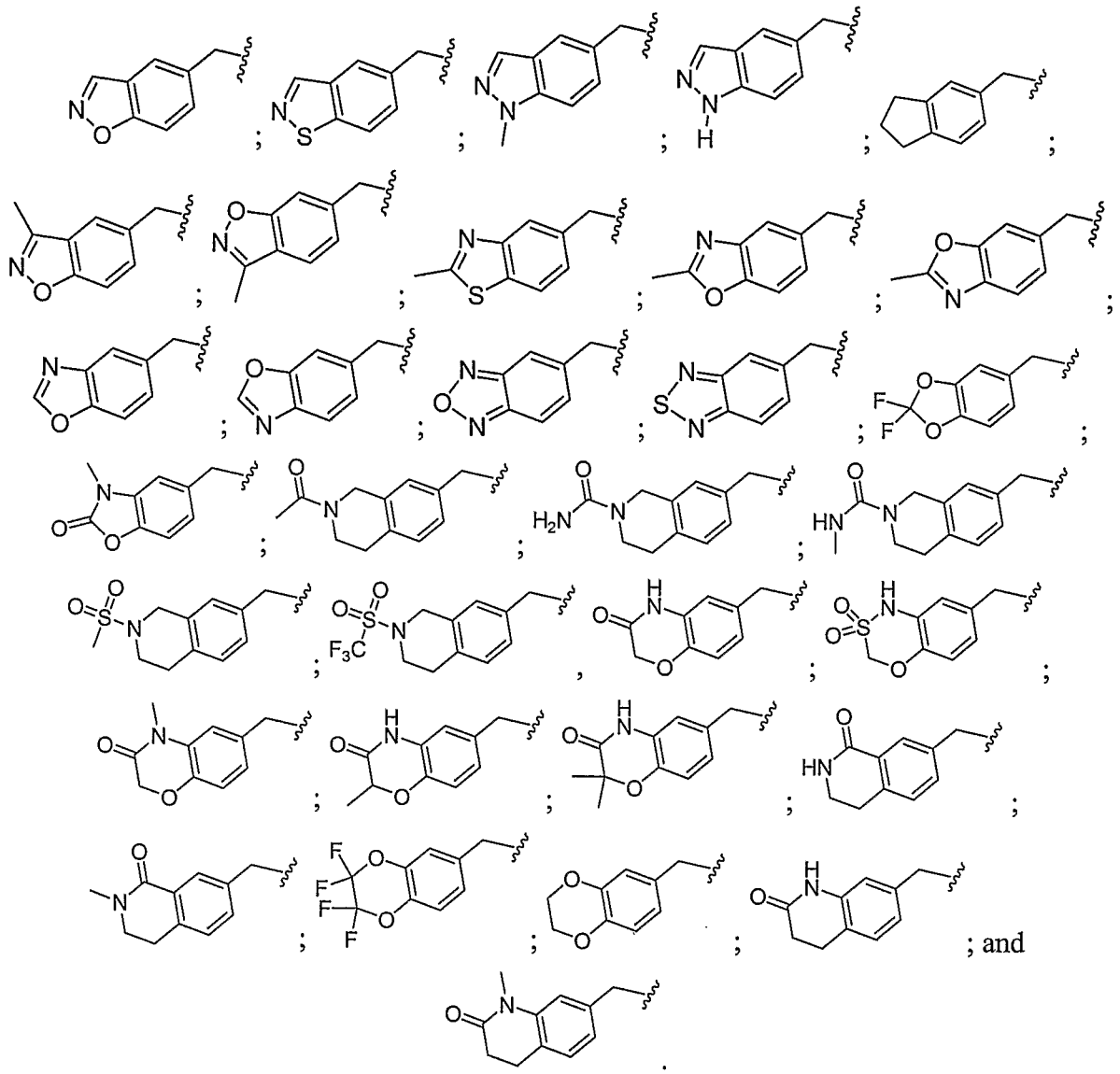


wherein all variables are as defined hereinabove.

For example, in some embodiments, R^1 of the structures of Groups IV(a) and (b) may be selected from Substituent Group 8 as defined hereinabove.

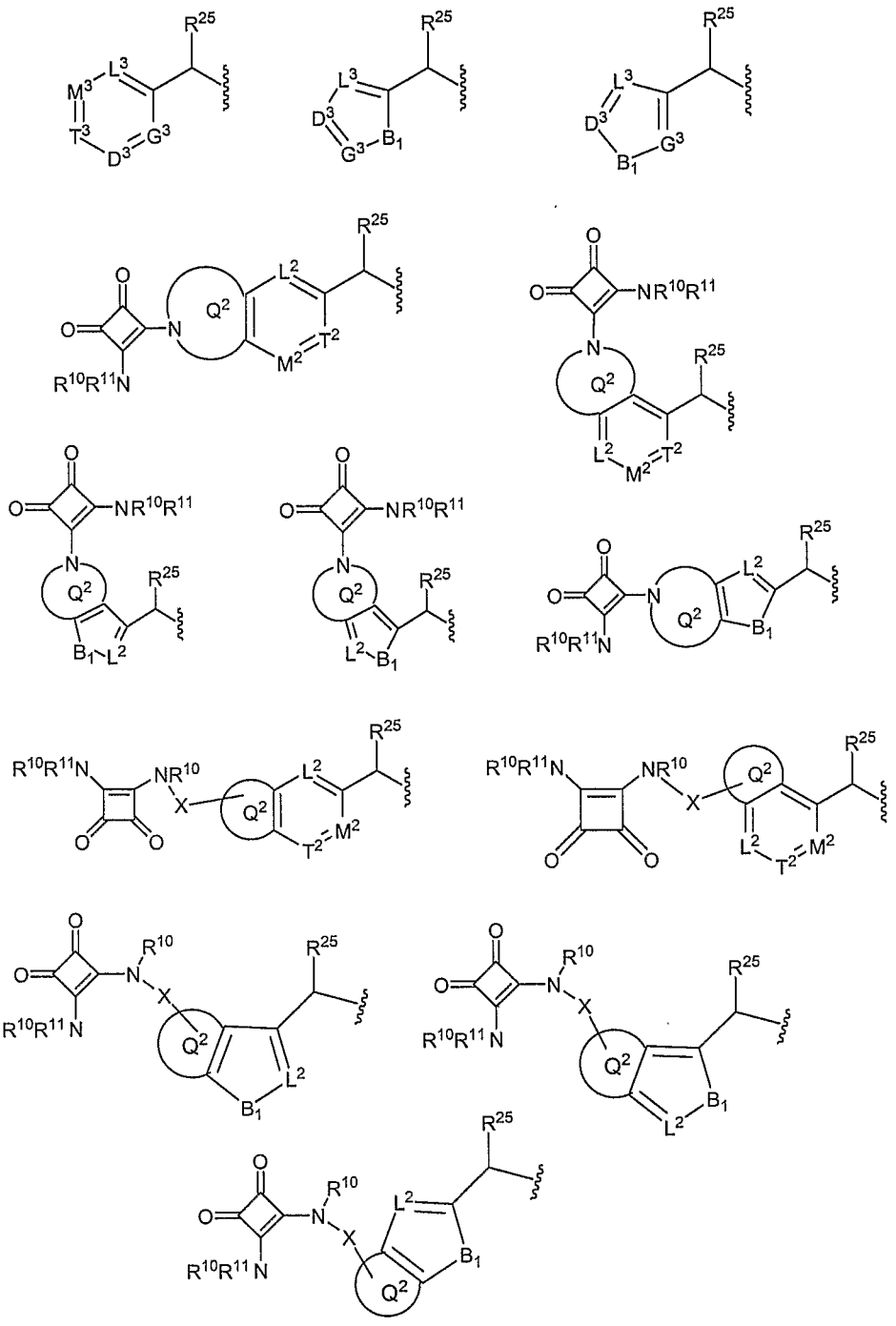
[0123] In yet a further embodiment, R^1 of Formula (IV) may be selected from Substituent Group 9:





For example, in some embodiments, R^1 of the structures of Groups IV(a) and (b) may be selected from Substituent Group 9 as defined hereinabove.

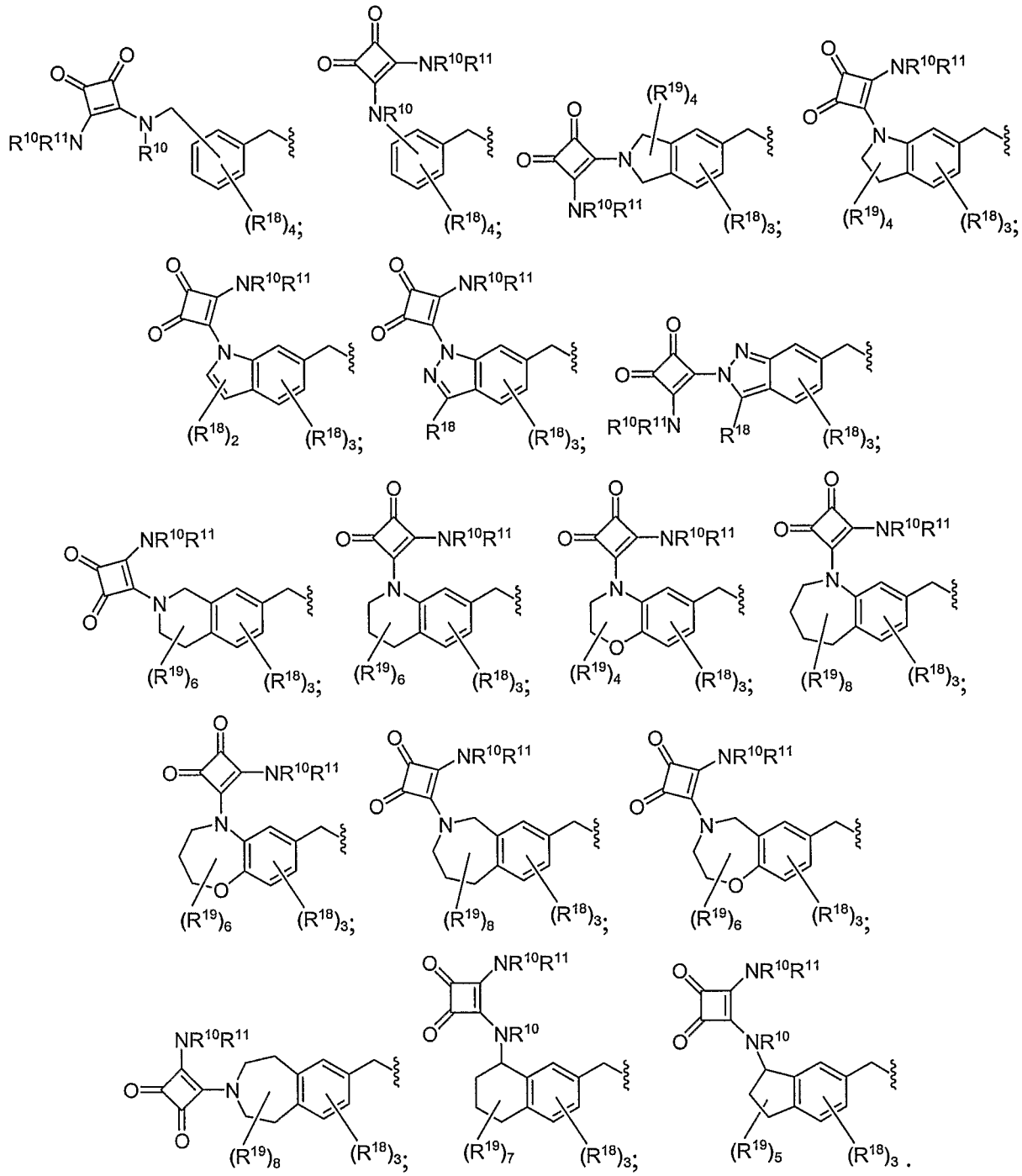
[0124] In still a further embodiment, R^1 of Formula (IV) may be selected from Substituent Group 10:



wherein all variables are as defined hereinabove.

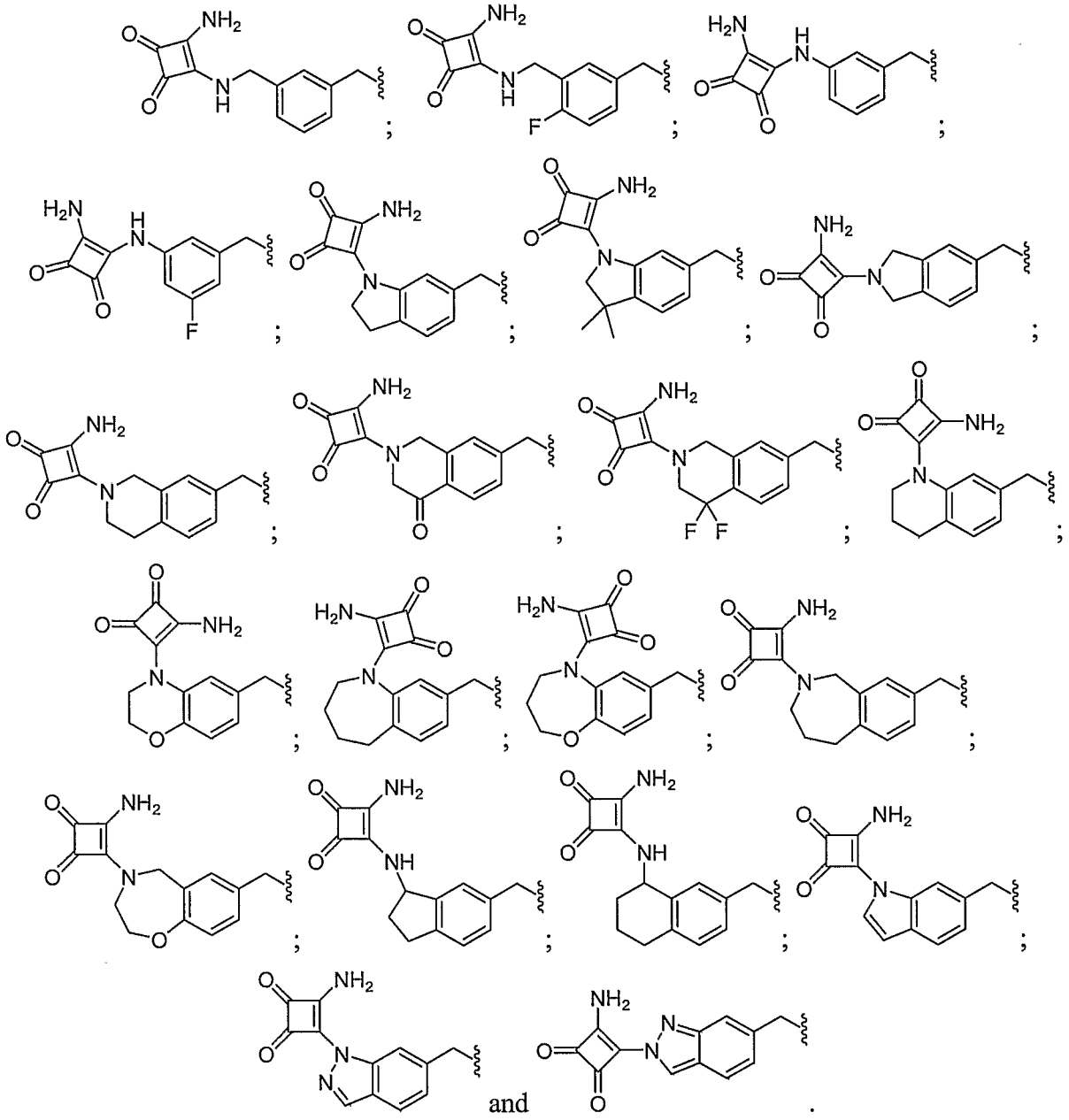
For example, in some embodiments, R^1 of the structures of Groups IV(a) and (b) may be selected from Substituent Group 10 as defined hereinabove.

[0125] In one embodiment, R^1 of Formula (IV) may be selected from Substituent Group 11:



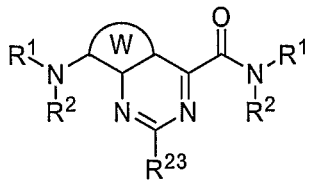
For example, in some embodiments, R^1 of the structures of Groups IV(a) and (b) may be selected from Substituent Group 11 as defined hereinabove.

[0126] In another embodiment, R^1 of Formula (IV) may be selected from Substituent Group 12:



For example, in some embodiments, R^1 of the structures of Groups IV(a) and (b) may be selected from Substituent Group 12 as defined hereinabove.

[0127] In still another embodiment of the present invention, the amide containing heterobicyclic metalloprotease compounds may be represented by the general Formula (V):



Formula (V)

and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof,

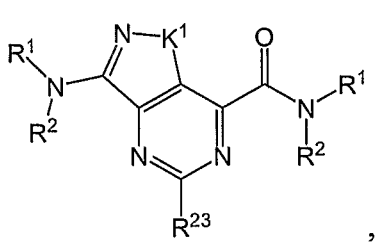
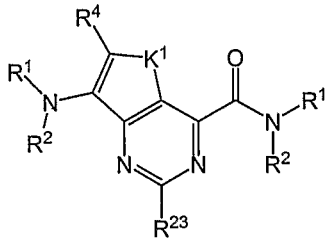
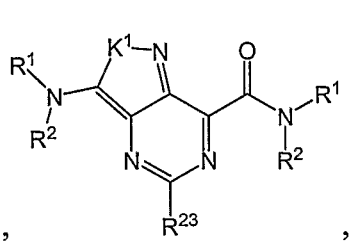
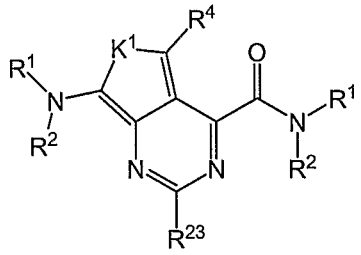
wherein:

R^1 in each occurrence may be the same or different and is as defined hereinabove;

R^2 in each occurrence may be the same or different and is as defined hereinabove; and

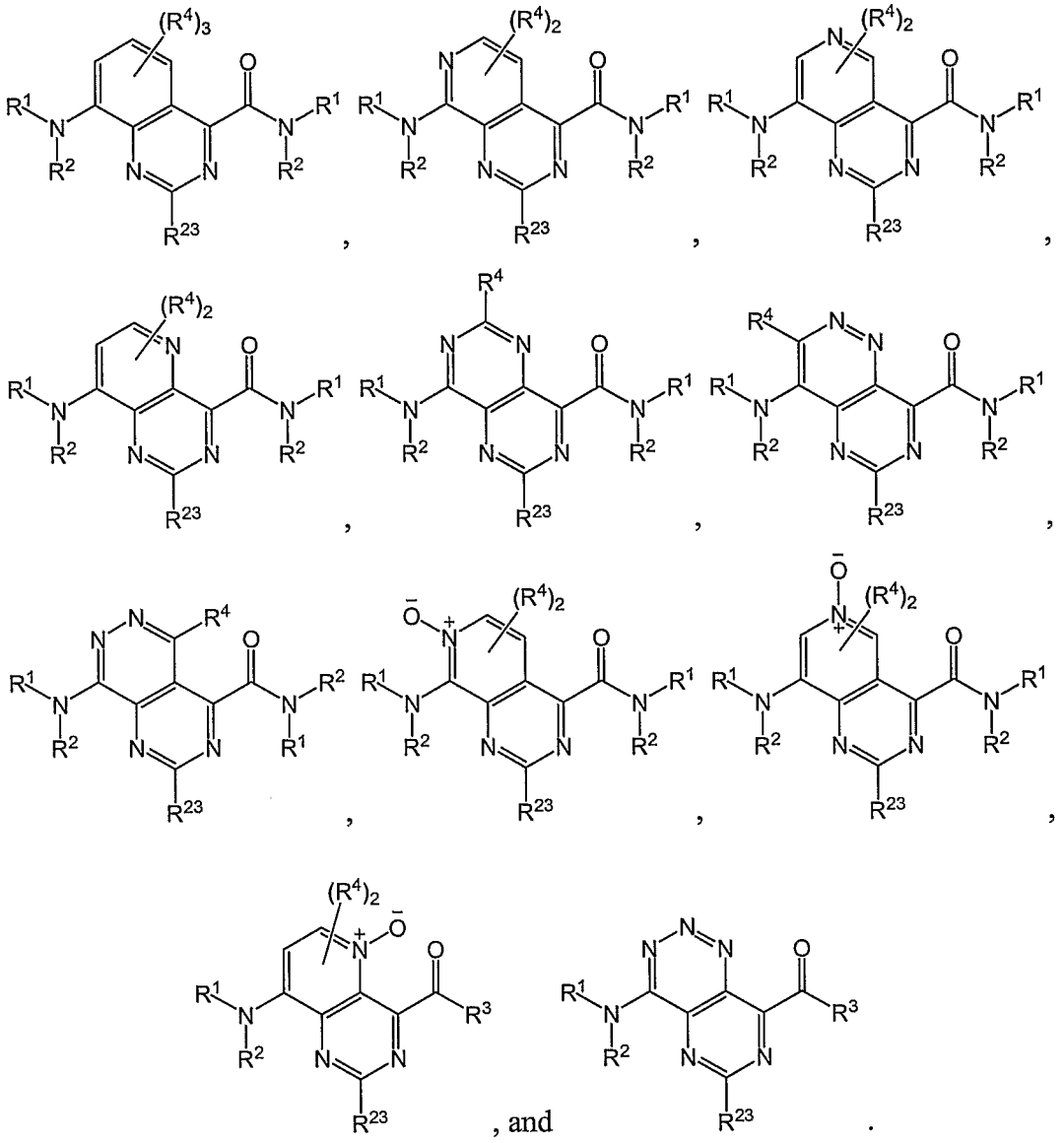
all remaining variables are as defined hereinabove.

[0128] In a further embodiment, compounds of Formula (V) may be selected from Group V(a):

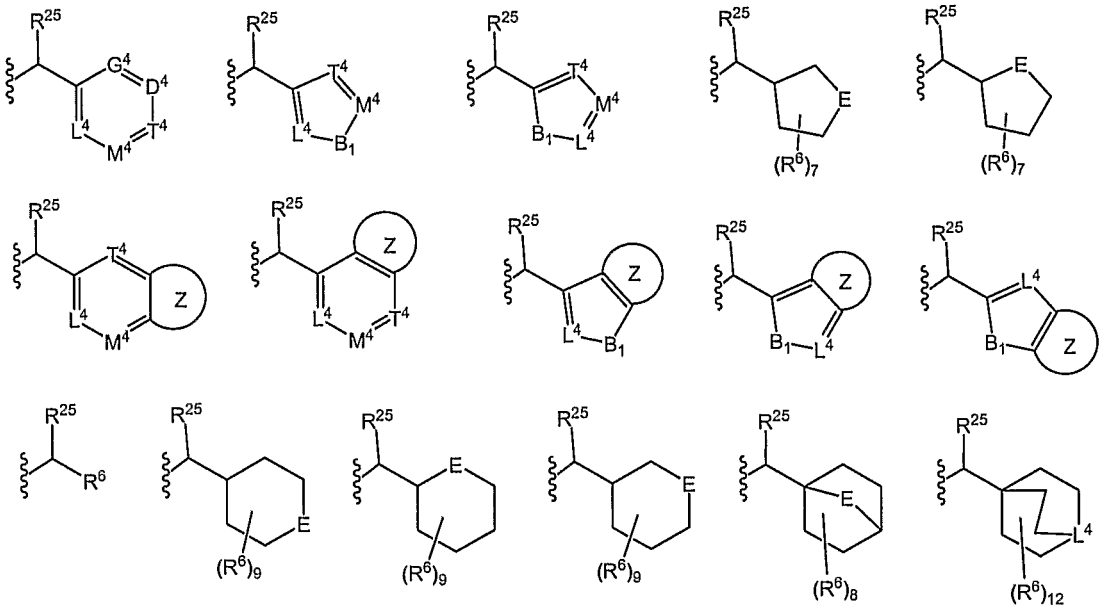

,

,

, and


wherein all variables are as defined hereinabove.

[0129] In yet a further embodiment, the compounds of Formula (V) may be selected from Group V(b):



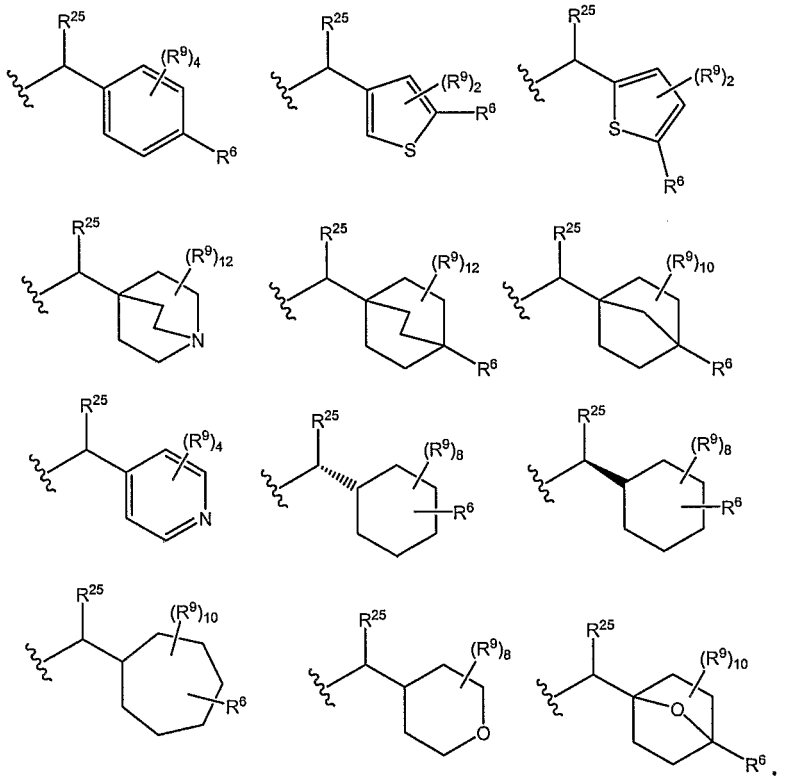
[0130] In still a further embodiment, at least one R^1 of Formula (V) may be selected from Substituent Group 13:



wherein all variables are as defined hereinabove.

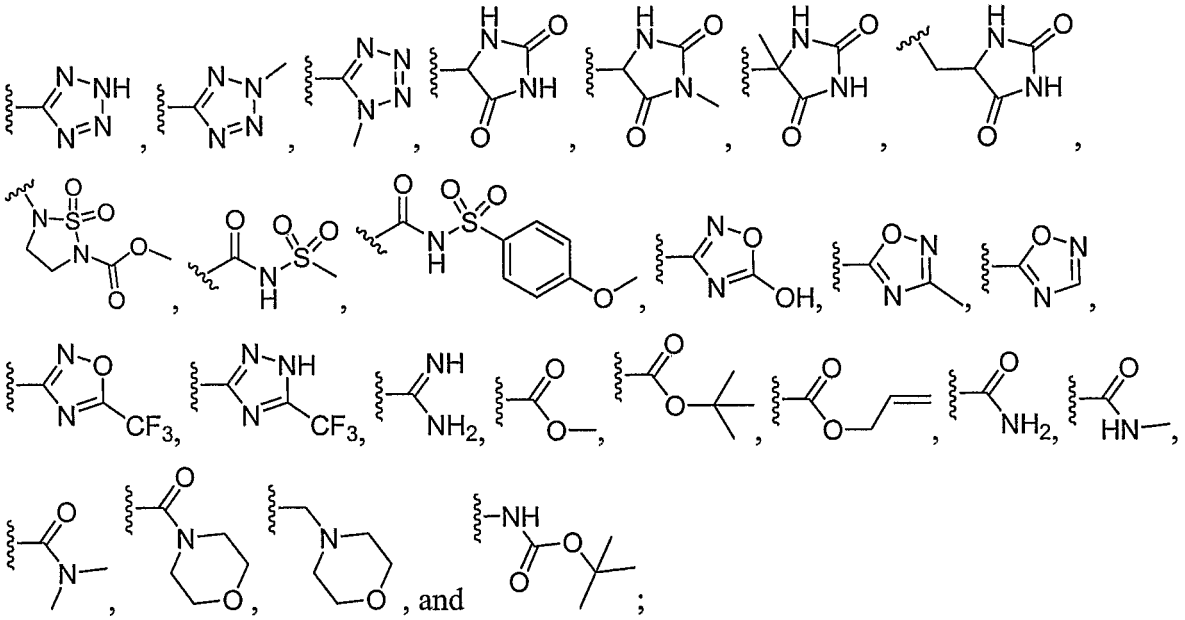
For example, in some embodiments, at least one R^1 of the structures of Groups V(a) and (b) may be selected from Substituent Group 13 as defined hereinabove.

[0131] In one embodiment, at least one R^1 of the compounds of Formula (V) may be selected from Substituent Group 14:



For example, in some embodiments, at least one R^1 of the structures of Groups V(a) and (b) may be selected from Substituent Group 14 as defined hereinabove.

[0132] In another embodiment, R^6 of Substituent Group 14 may be selected from: hydrogen, halo, CN, OH, CH_2OH, CF_3, CHF_2, OCF_3, $OCHF_2$, $COCH_3$, SO_2CH_3, SO_2CF_3, SO_2NH_2, SO_2NHCH_3, $SO_2N(CH_3)_2$, NH_2, $NHCOCH_3$, $N(COCH_3)_2$, $NHCONH_2$, $NHSO_2CH_3$, alkoxy, alkyl, CO_2H,

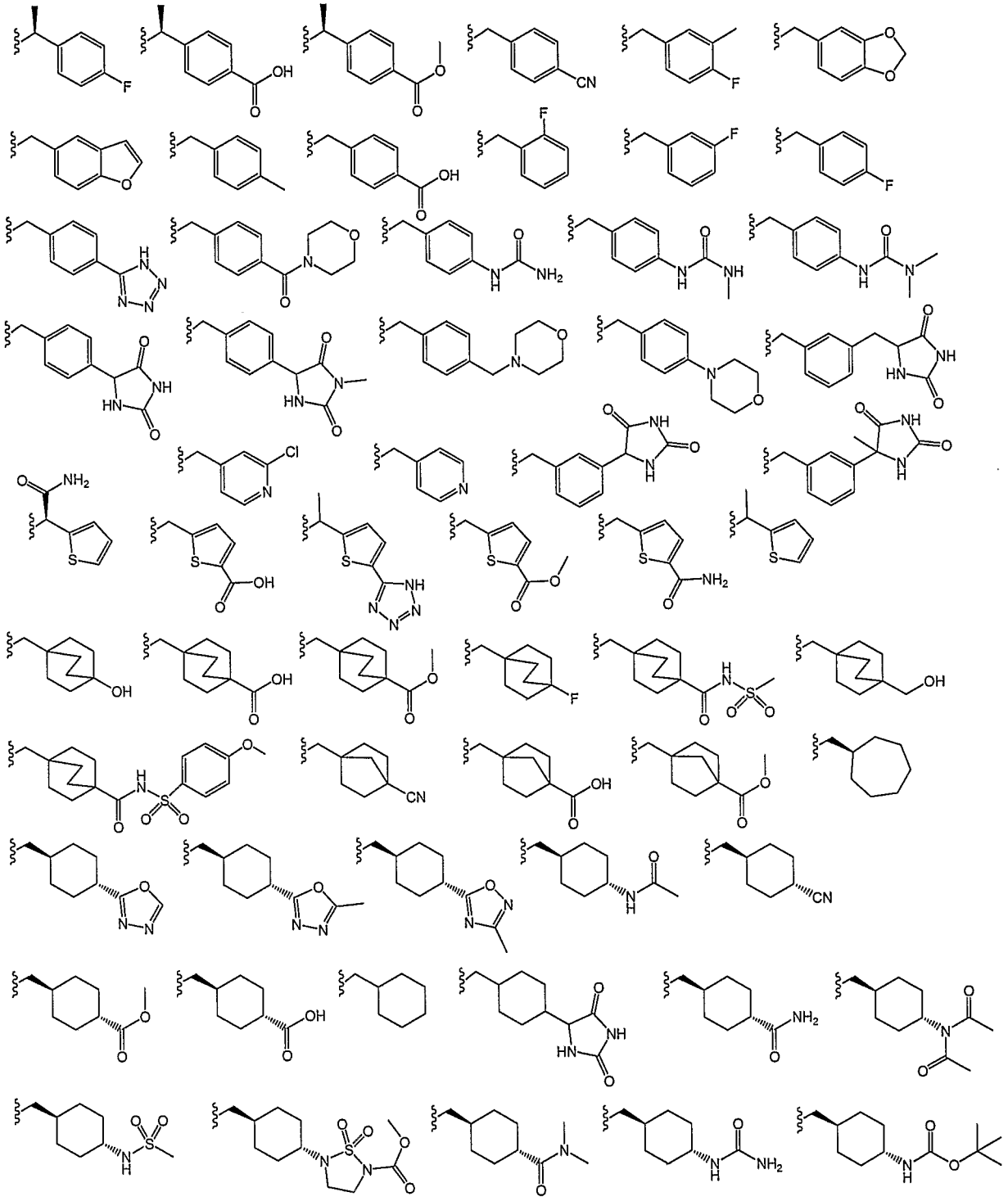


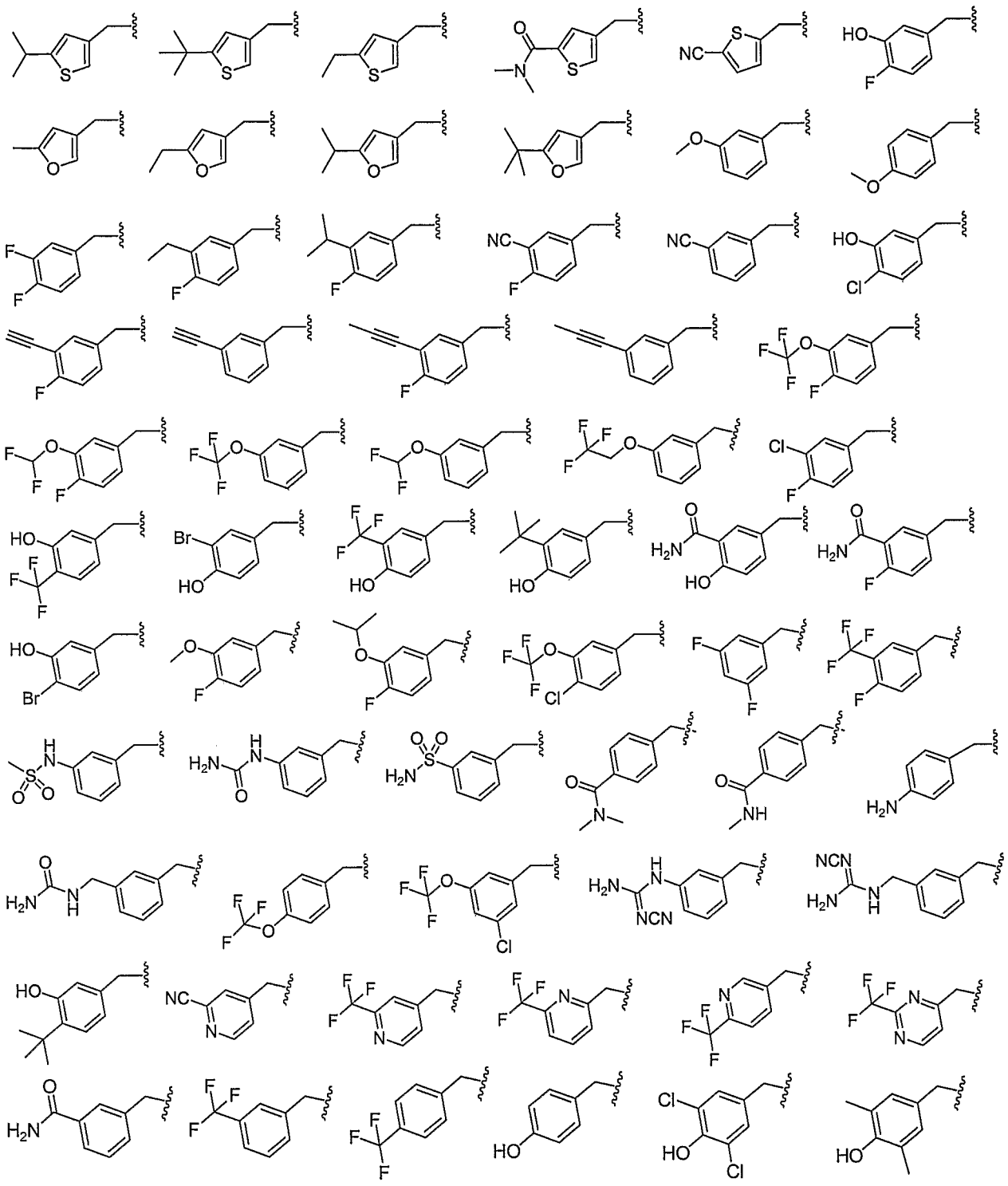
wherein

R^9 is independently selected of hydrogen, fluoro, chloro, CH_3, CF_3, CHF_2, OCF_3, and $OCHF_2$;

R^{25} is selected of hydrogen, CH_3, COOMe, COOH, and $CONH_2$.

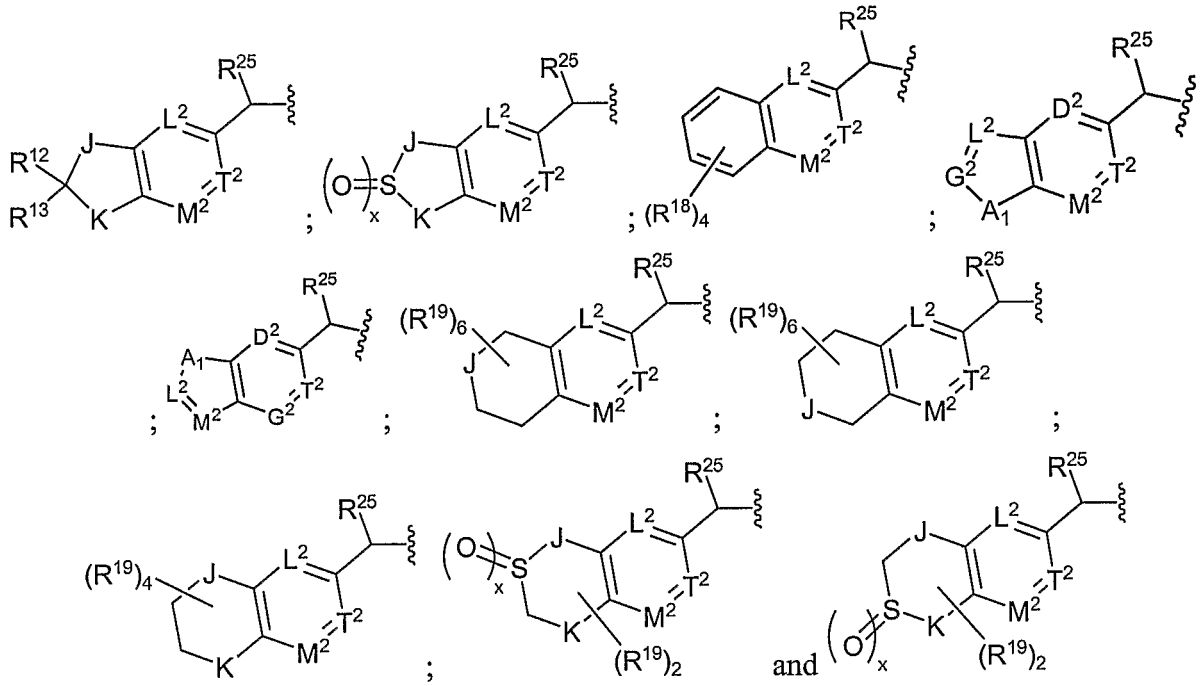
[0133] In yet another embodiment, at least one R^1 of Formula (V) may be selected from Substituent Group 15:





For example, in some embodiments, at least one R^1 of the structures of Groups V(a) and (b) may be selected from Substituent Group 15 as defined hereinabove.

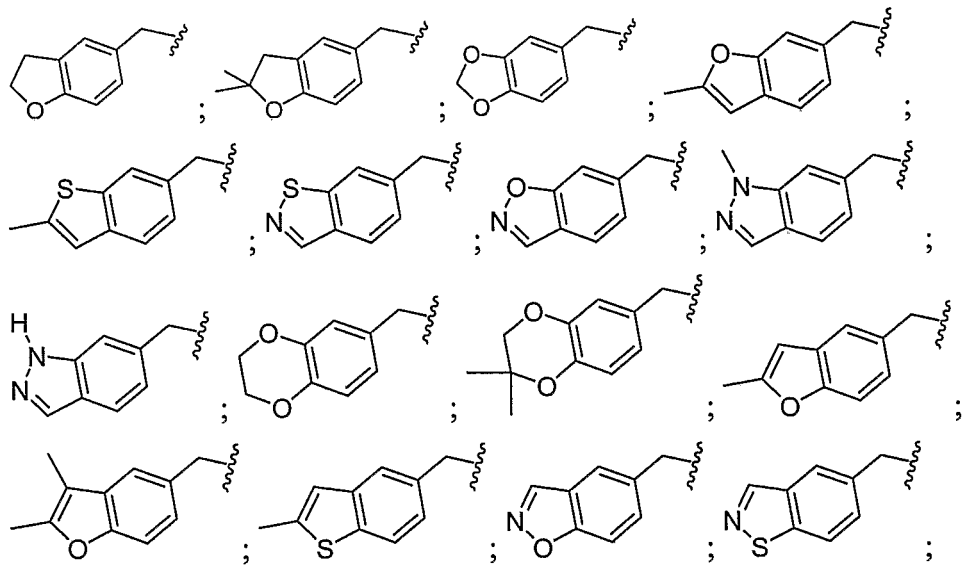
[0134] In still another embodiment, at least one R^1 of Formula (V) may be selected from Substituent Group 8:

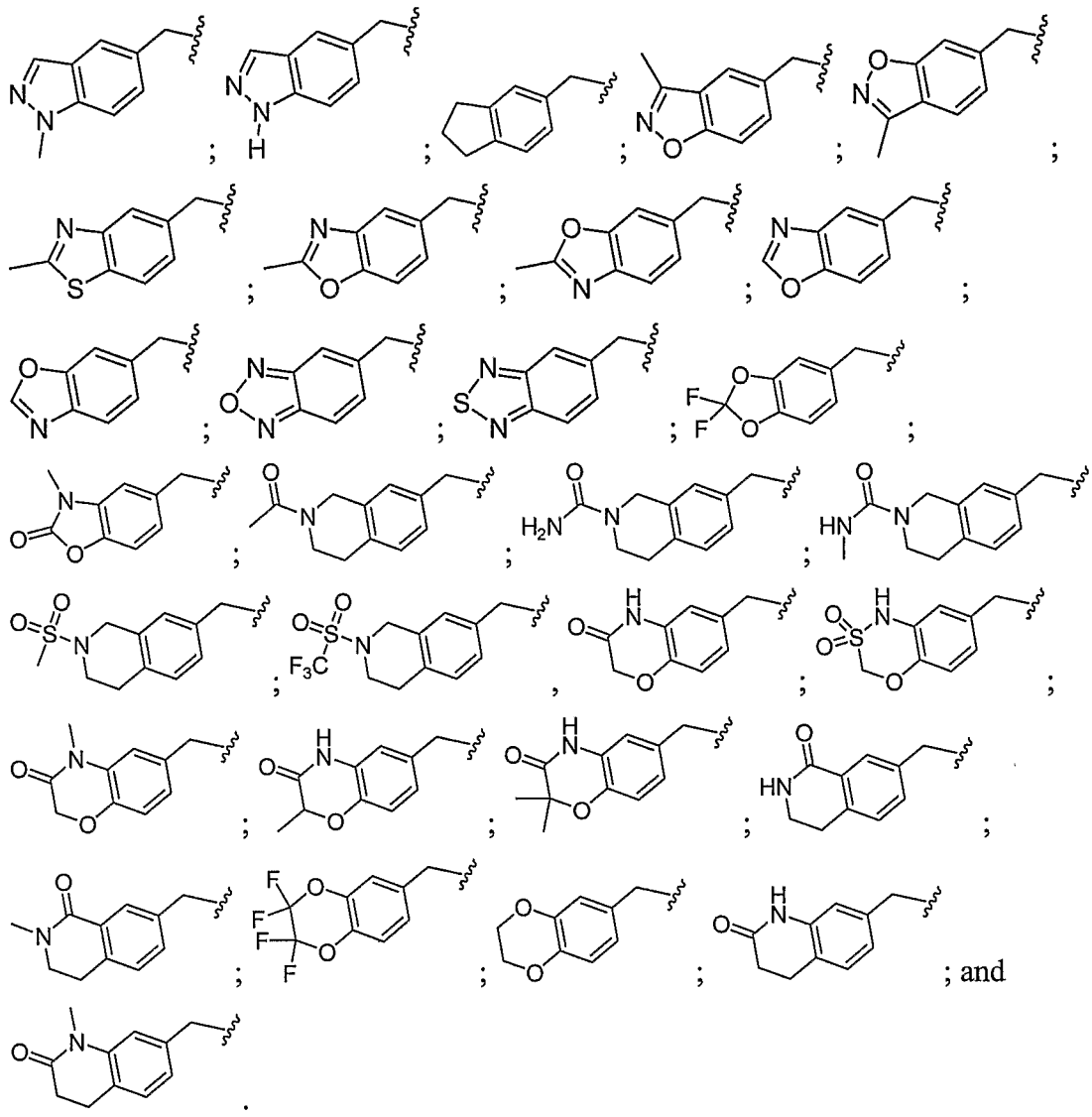


wherein all variables are as defined hereinabove.

For example, in some embodiments, at least one R^1 of the structures of Groups V(a) and (b) may be selected from Substituent Group 8 as defined hereinabove.

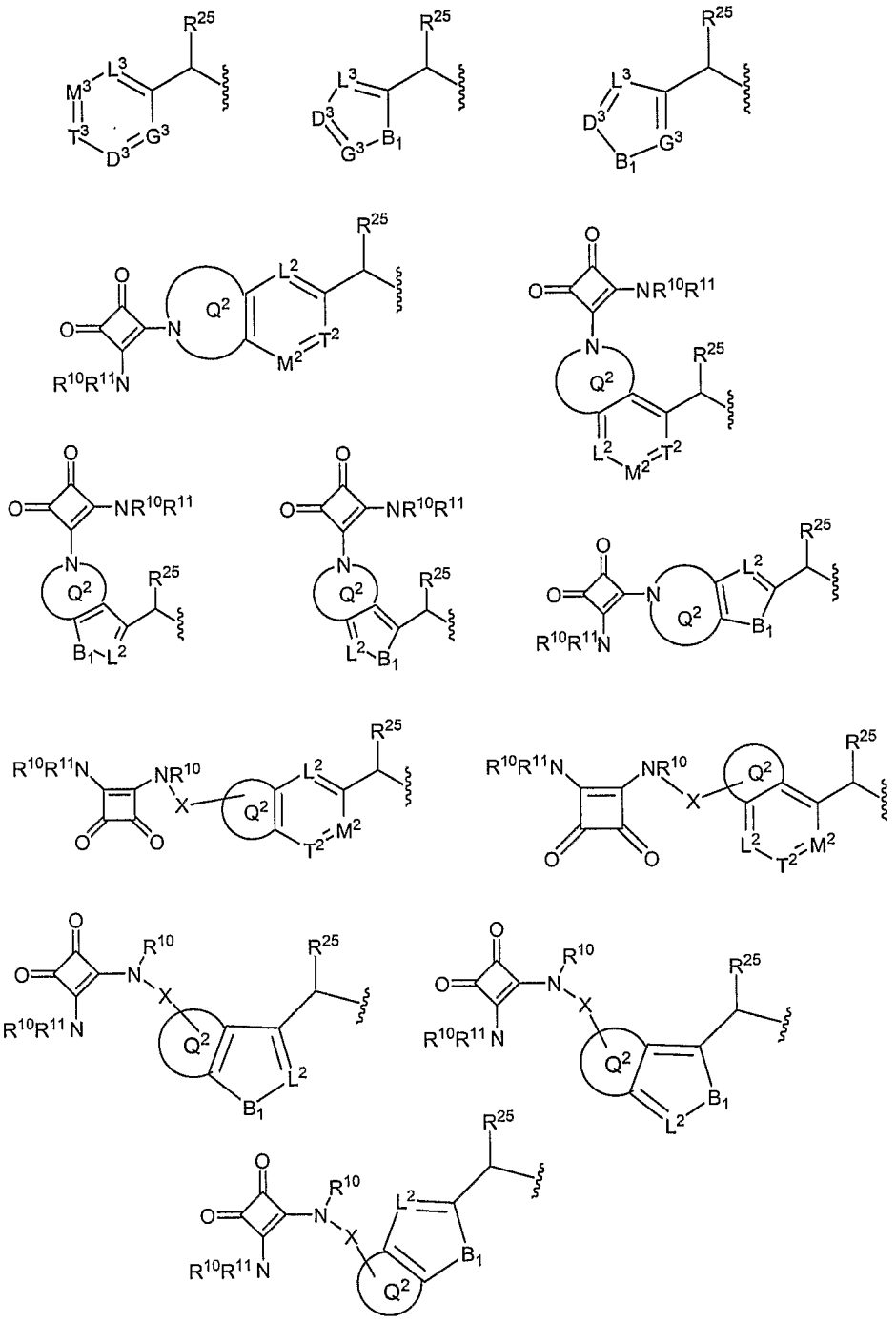
[0135] In a further embodiment, at least one R^1 of Formula (V) may be selected from Substituent Group 9:





For example, in some embodiments, at least one R^1 of the structures of Groups V(a) and (b) may be selected from Substituent Group 9 as defined hereinabove.

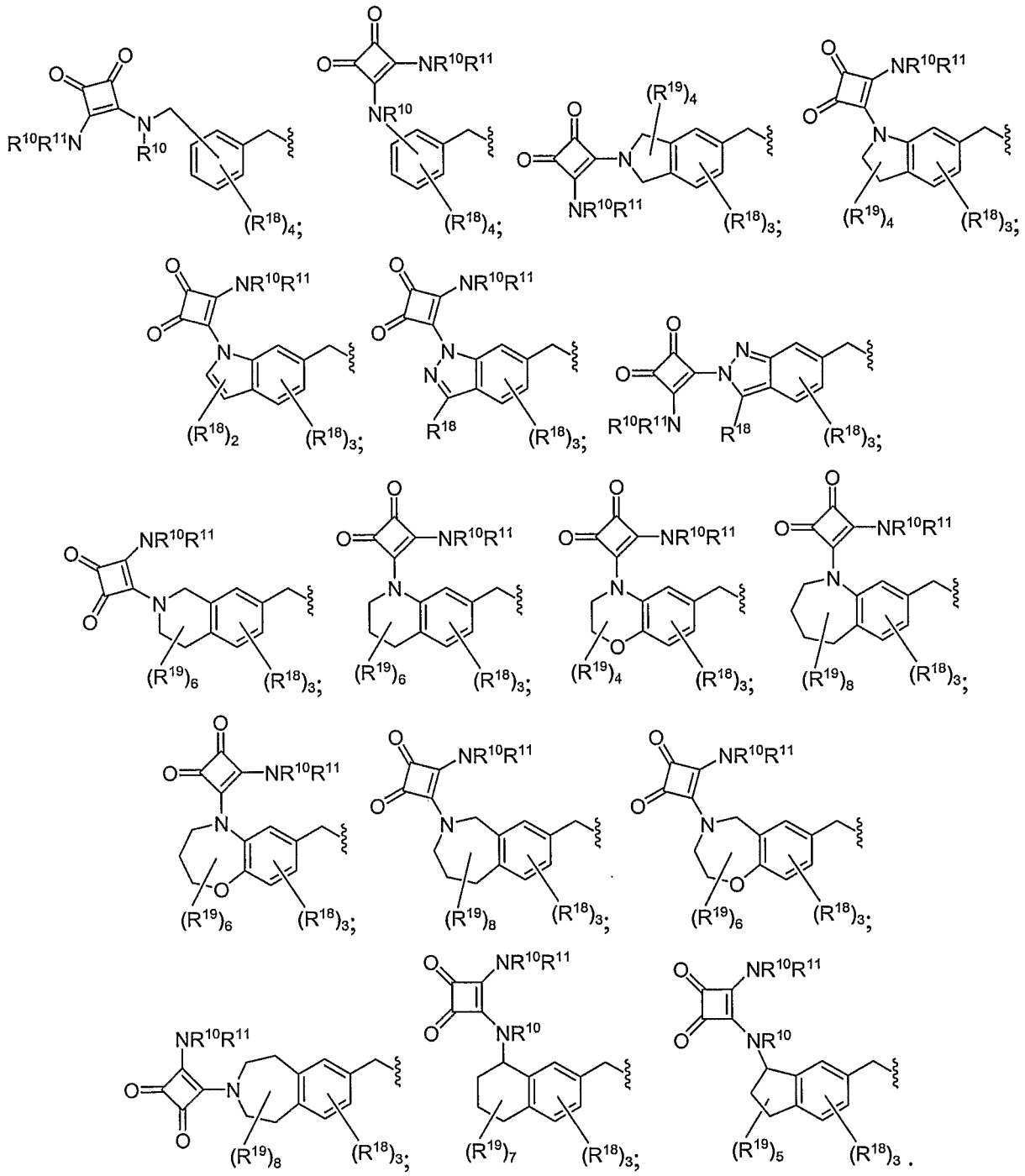
[0136] In yet a further embodiment, one R^1 of Formula (V) may be selected from Substituent Group 10:



wherein all variables are as defined hereinabove.

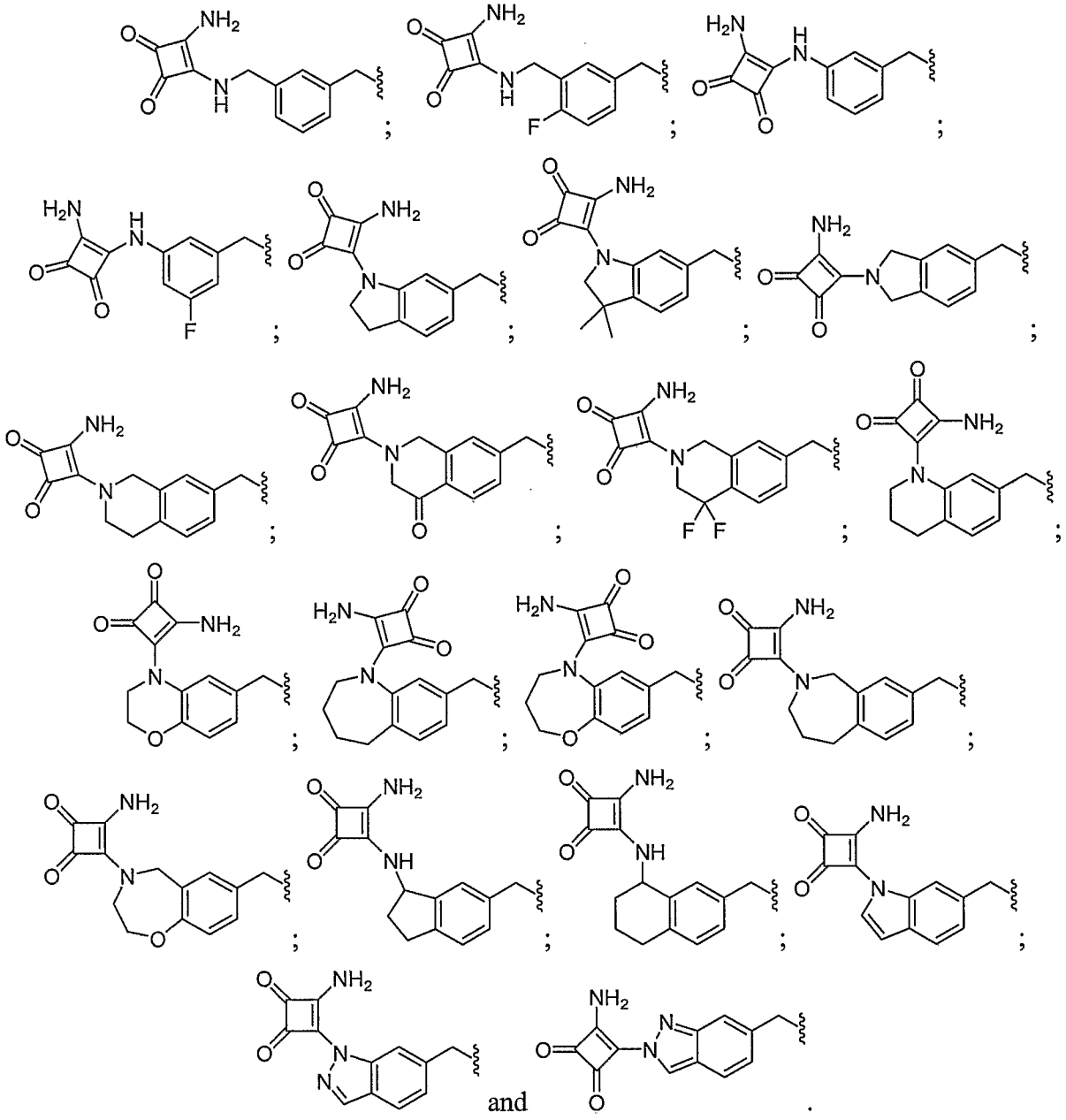
For example, in some embodiments, one R^1 of the structures of Groups V(a) and (b) may be selected from Substituent Group 10 as defined hereinabove.

[0137] In still a further embodiment, each R^1 of Formula (V) may be independently selected from Substituent Group 11:



For example, in some embodiments, one R^1 of the structures of Groups V(a) and (b) may be selected from Substituent Group 11 as defined hereinabove.

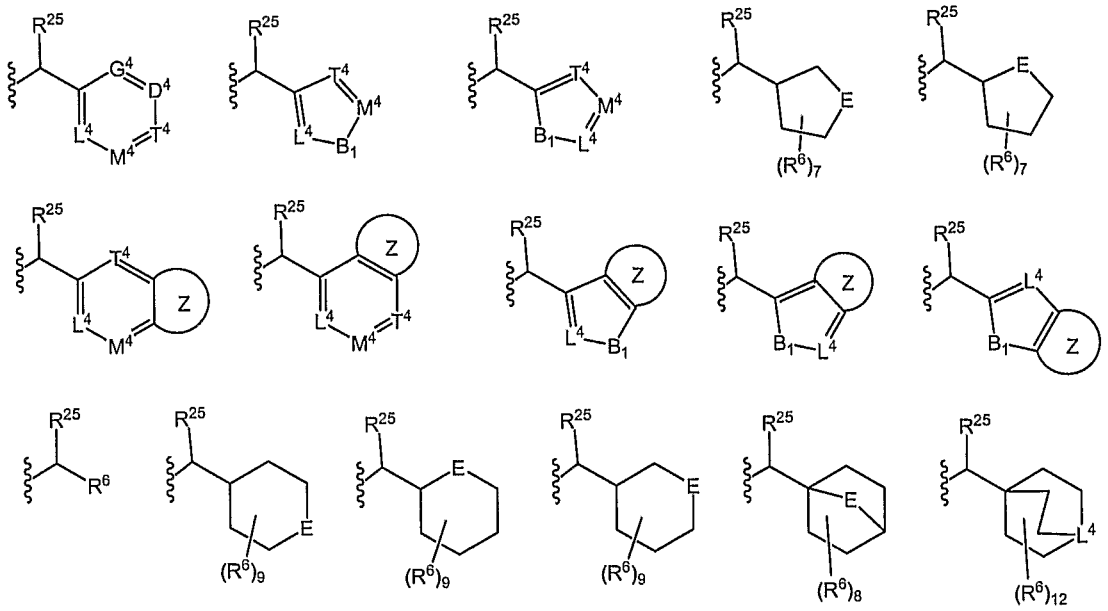
[0138] In one embodiment, one R^1 of Formula (V) may be selected from Substituent Group 12:



For example, in some embodiments, one R^1 of the structures of Groups V(a) and (b) may be selected from Substituent Group 12 as defined hereinabove.

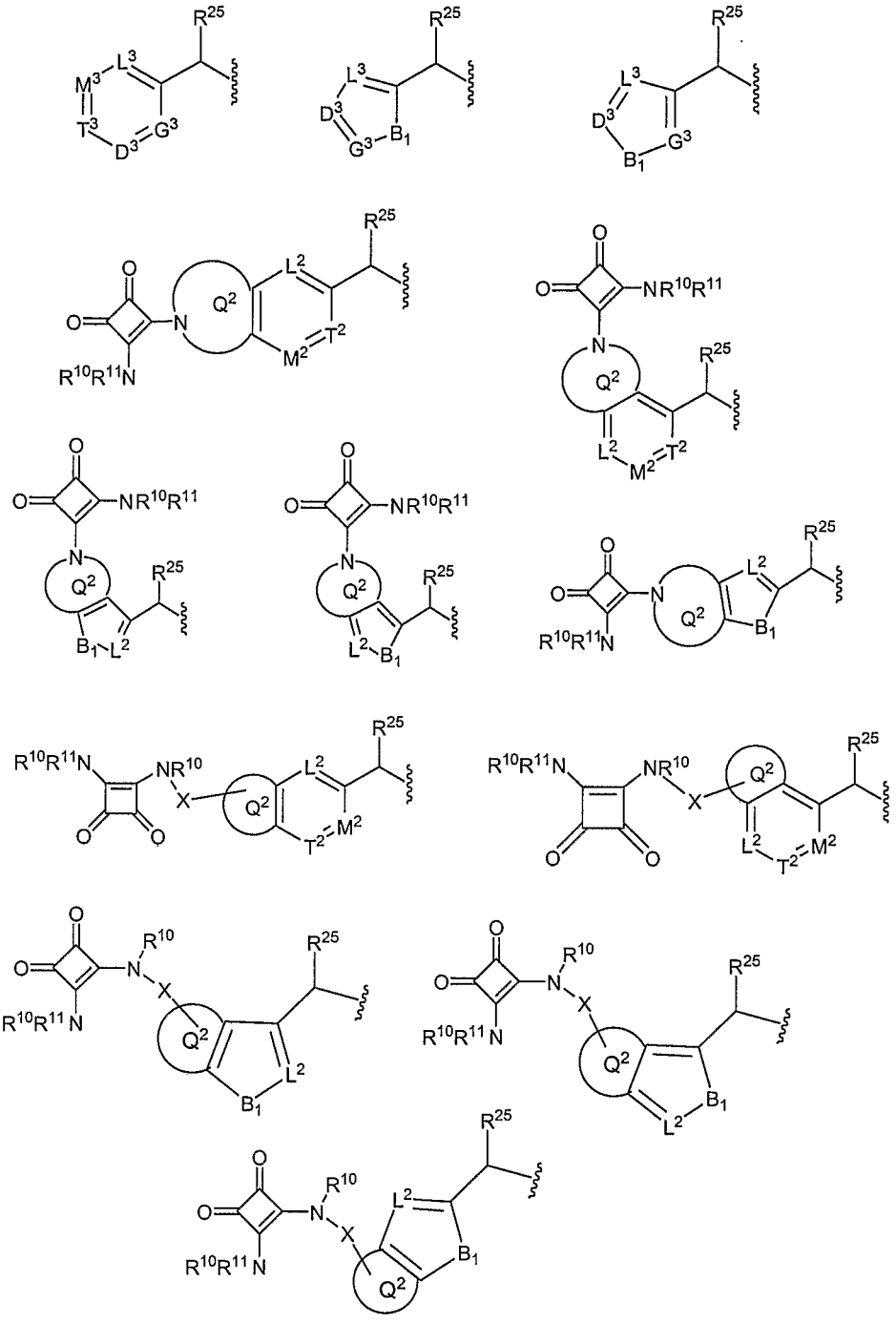
In some embodiments:

A) the first occurrence of R^1 of Formula (V) is selected from Substituent Group 13:



; and

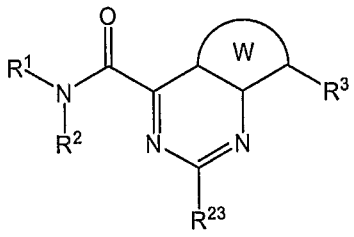
B) the second occurrence of R^1 of Formula (V) is selected from Substituent Group 10:



wherein all variables are as defined hereinabove.

For example in some embodiments, the first occurrence of R^1 of the structures of Groups V(a) and (b) may be selected from Substituent Group 13 as defined hereinabove, and the second occurrence of R^1 of the structures of Groups V(a) and (b) may be selected from Substituent Group 10 as defined hereinabove.

[0139] In another embodiment of the present invention, the amide containing heterobicyclic metalloprotease compounds may be represented by the general Formula (VI):

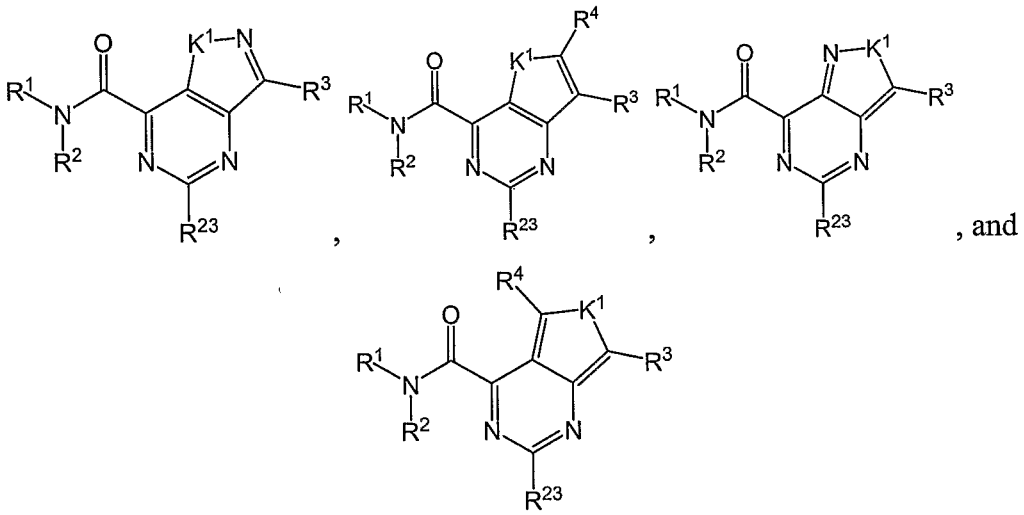


Formula (VI)

and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof,

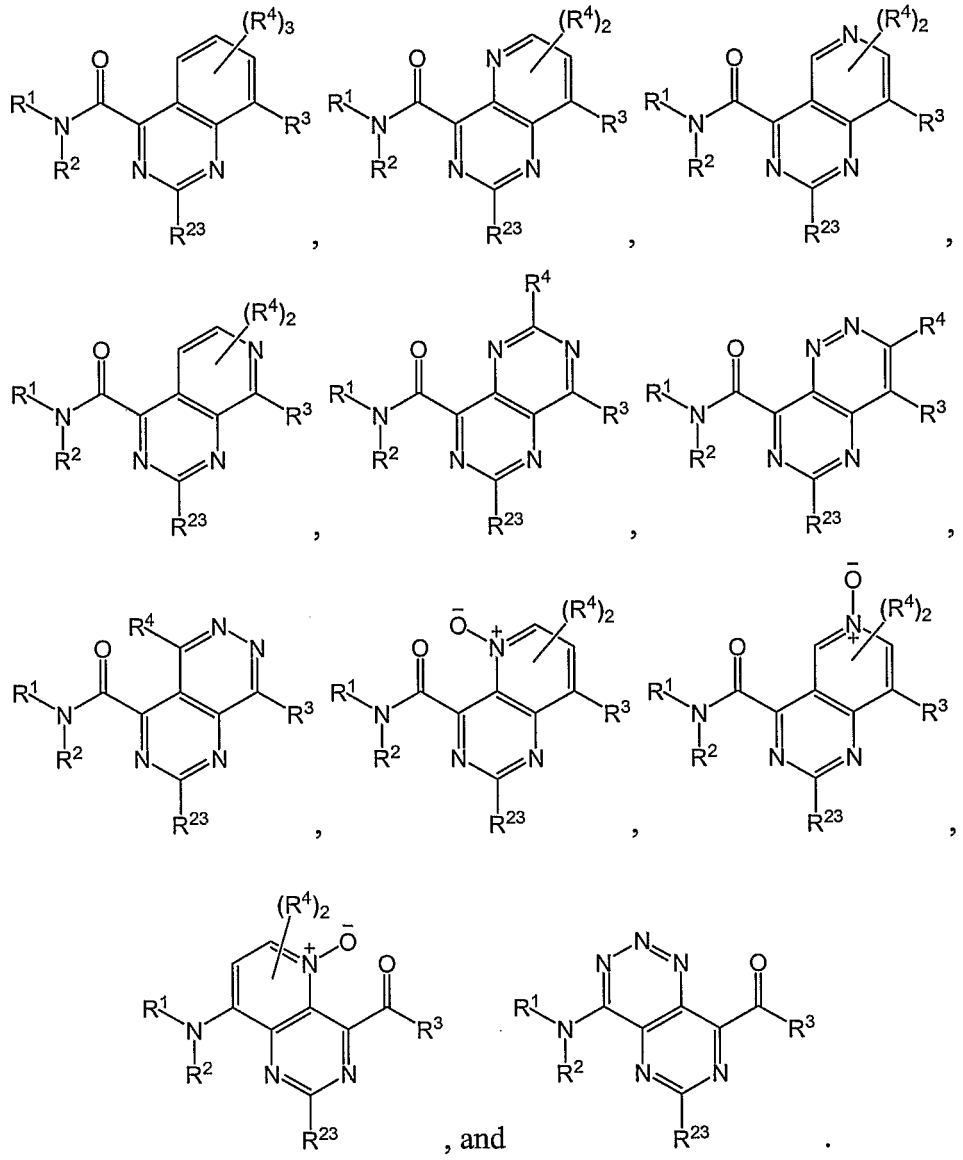
wherein all variables are as defined hereinabove.

[0140] In yet another embodiment, the compounds of Formula (VI) may be selected from Group VI(a):

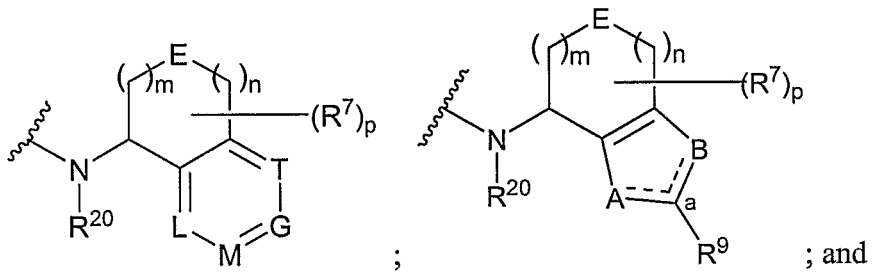


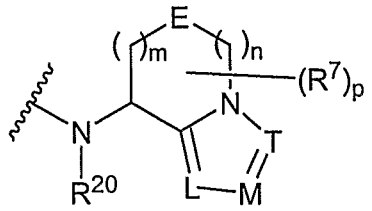
wherein all variables are as defined hereinabove.

[0141] In still another embodiment, the compounds of Formula (VI) may be selected from Group VI(b):



[0142] In a further embodiment, R^3 of Formula (VI) may be selected from Substituent Group 1:

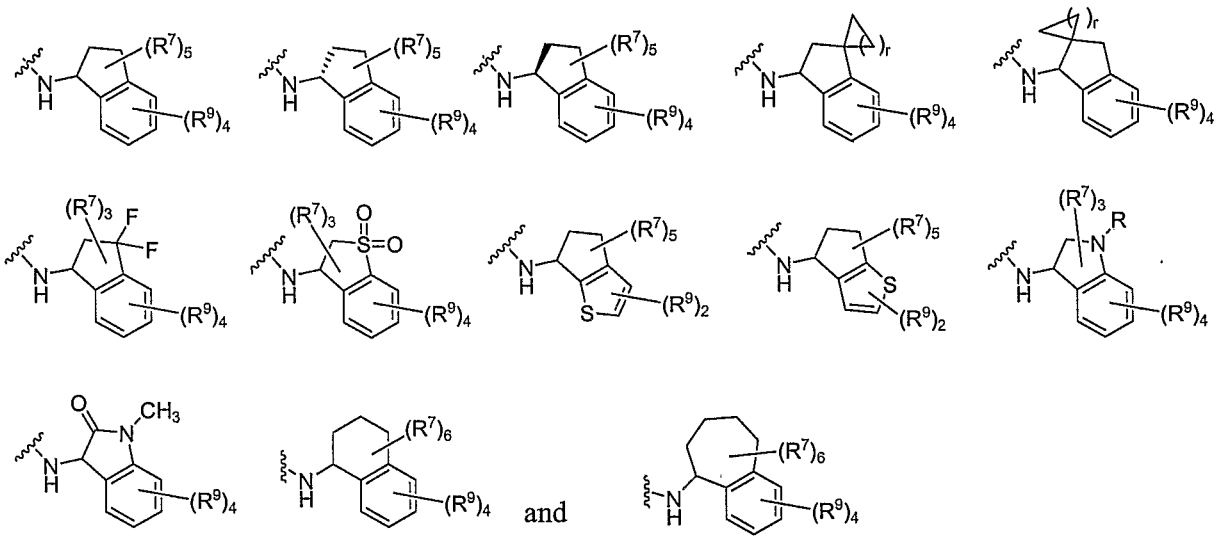




wherein all variables are as defined hereinabove.

For example, in some embodiments, R^3 of the structures of Groups VI(a) and (b) may be selected from Substituent Group 1 as defined hereinabove.

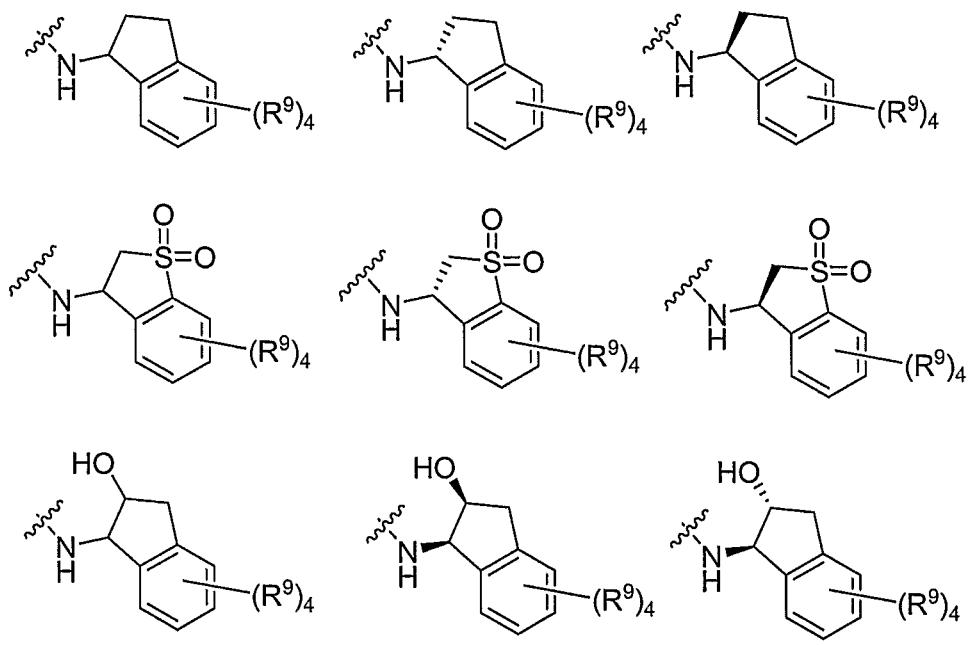
[0143] In yet a further embodiment, R^3 of Formula (VI) may be selected from Substituent Group 2:



wherein all variables are as defined hereinabove.

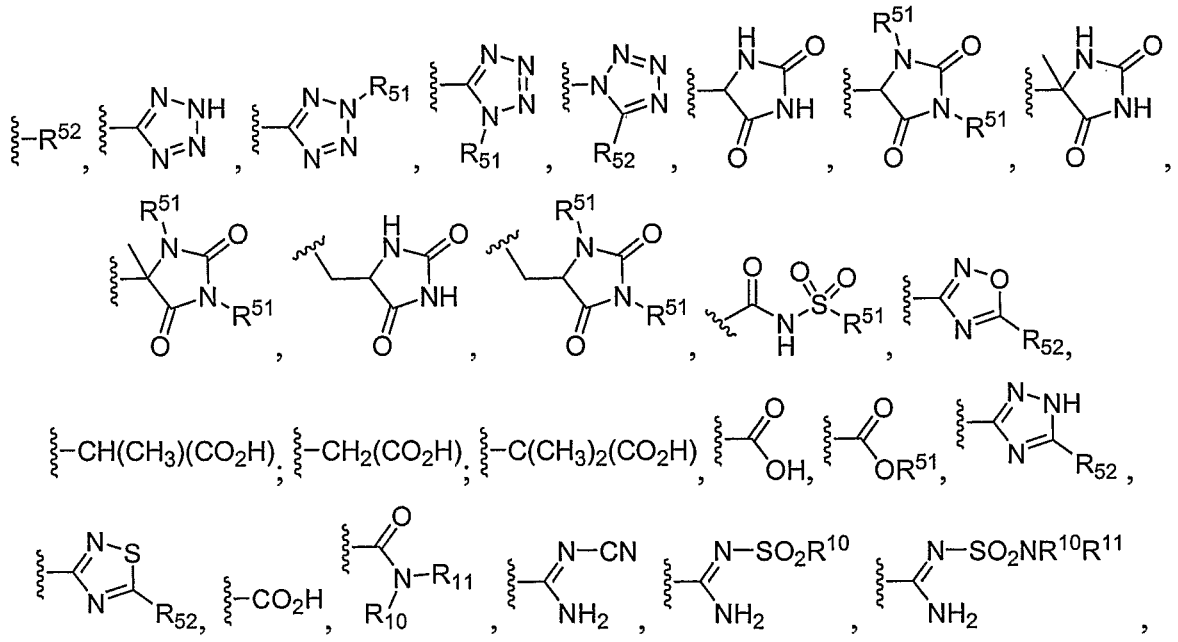
For example, in some embodiments, in some embodiments, R^3 of the structures of Groups VI(a) and (b) may be selected from Substituent Group 2 as defined hereinabove.

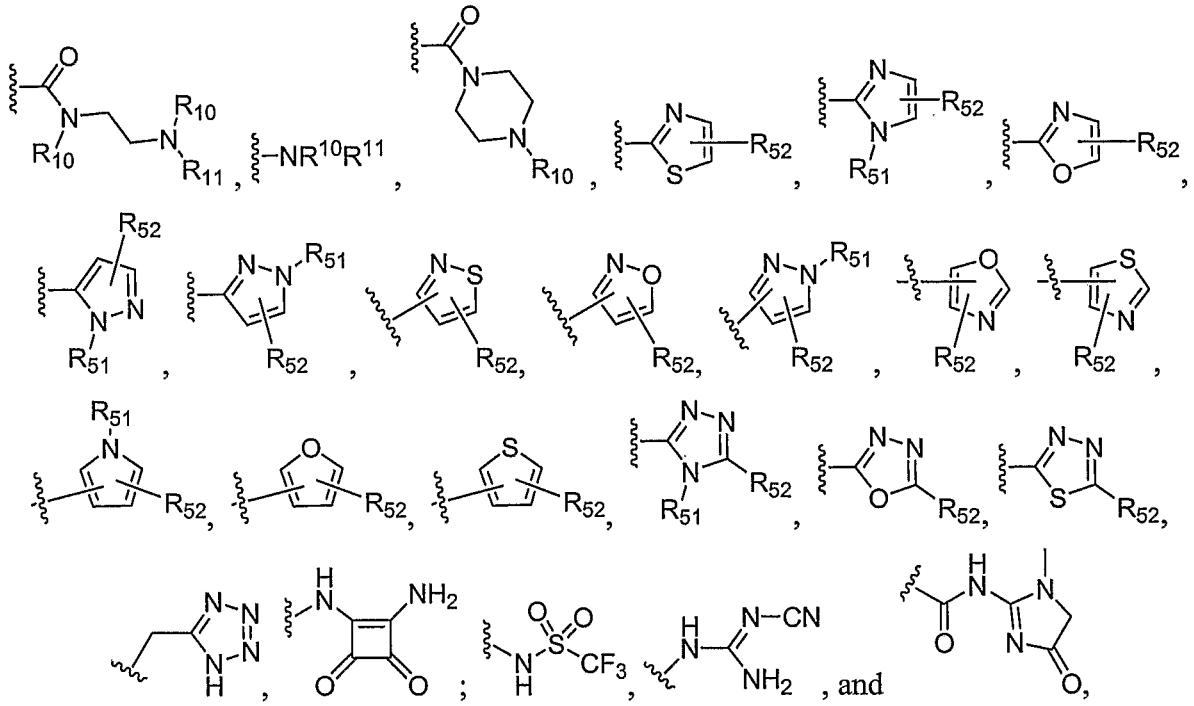
[0144] In still a further embodiment, R^3 of Formula (VI) may be selected from Substituent Group 3:



For example, in some embodiments, R^3 of the structures of Groups VI(a) and (b) may be selected from Substituent Group 3 as defined hereinabove.

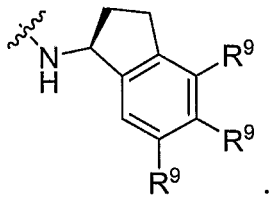
[0145] In one embodiment, each R^9 of Substituent Group 3 may independently be selected from:





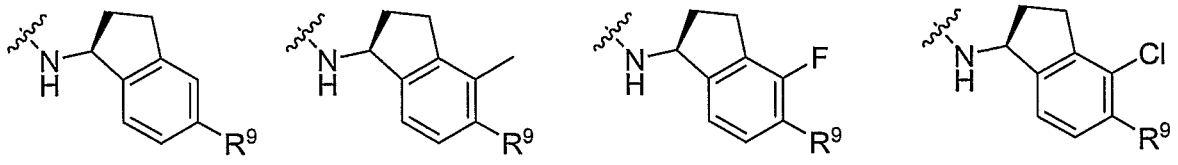
wherein all variables are as defined hereinabove.

[0146] In another embodiment, R^3 of Formula (VI) may be Substituent Group 16:

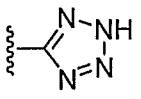
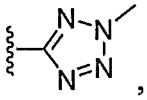
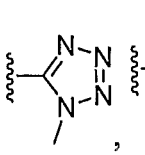
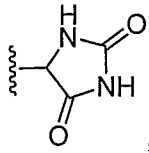
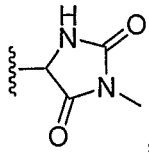
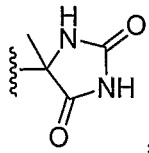
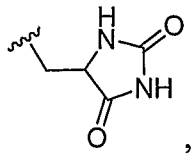
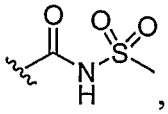
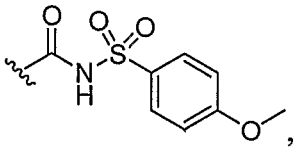
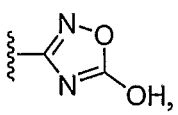
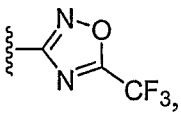
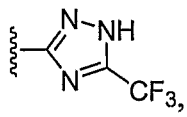
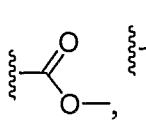
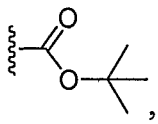
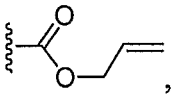
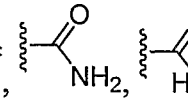
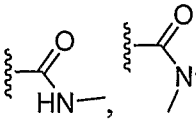
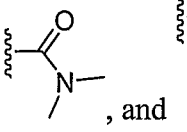
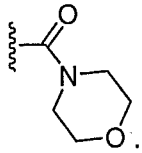


For example, in some embodiments, R^3 of the structures of Groups VI(a) and (b) may be selected from Substituent Group 16 as defined hereinabove.

[0147] In yet another embodiment, R^3 of Formula (VI) may be selected from Substituent Group 5:

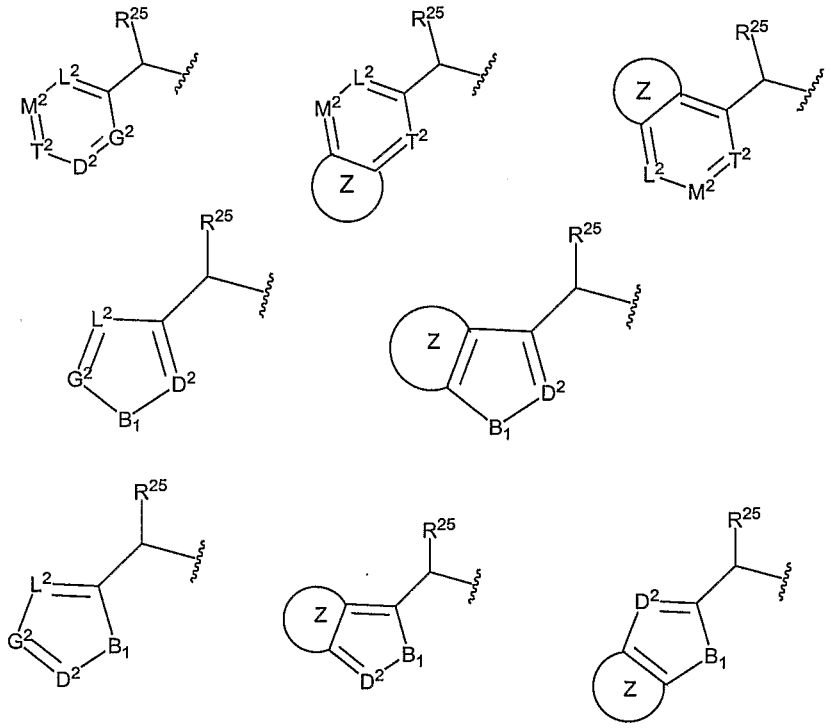


wherein:

R^9 is selected from hydrogen, fluoro, halo, CN, alkyl, CO_2H,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

For example, in some embodiments, R^3 of the structures of Groups VI(a) and (b) may be selected from Substituent Group 5 as defined hereinabove.

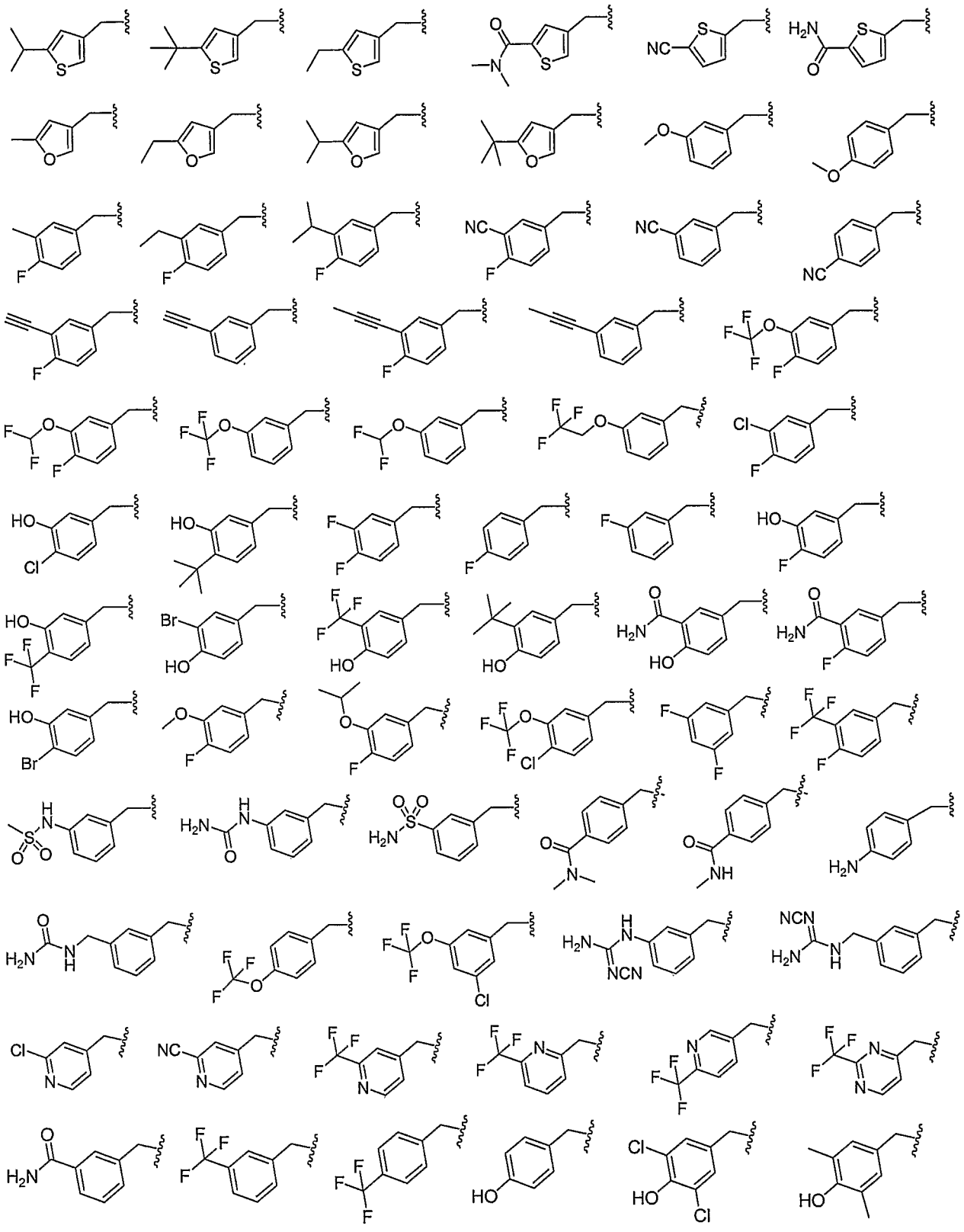
[0148] In still another embodiment, R^1 of the compounds of Formula (VI) may be selected from Substituent Group 6:



wherein all variables are as defined hereinabove.

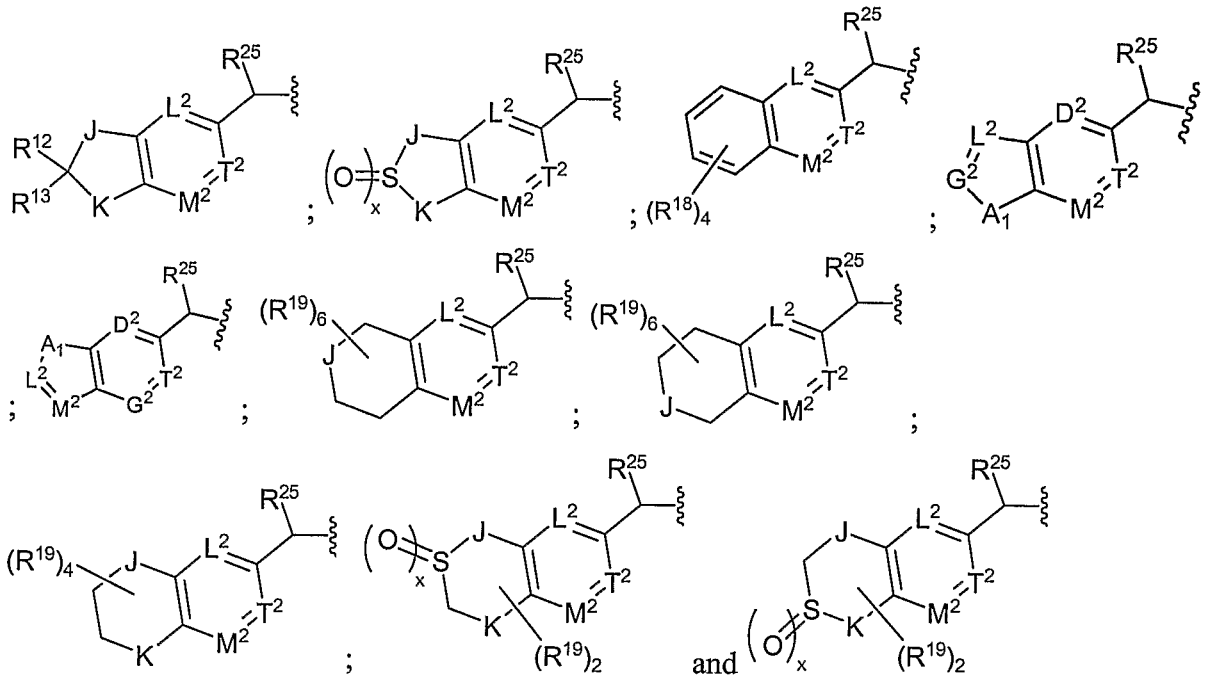
For example, in some embodiments, R^1 of the structures of Groups VI(a) and (b) may be selected from Substituent Group 6 as defined hereinabove.

[0149] In a further embodiment, R^1 of Formula (VI) may be selected from Susbstituent Group 7:



For example, in some embodiments, R^1 of the structures of Groups VI(a) and (b) may be selected from Substituent Group 7 as defined hereinabove.

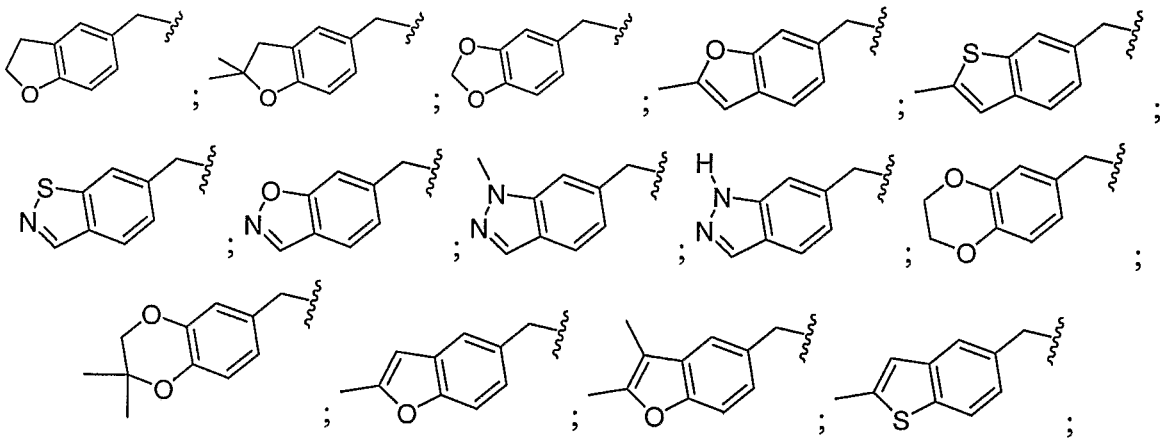
[0150] In yet a further embodiment, R^1 of Formula (VI) may be selected from Substituent Group 8:

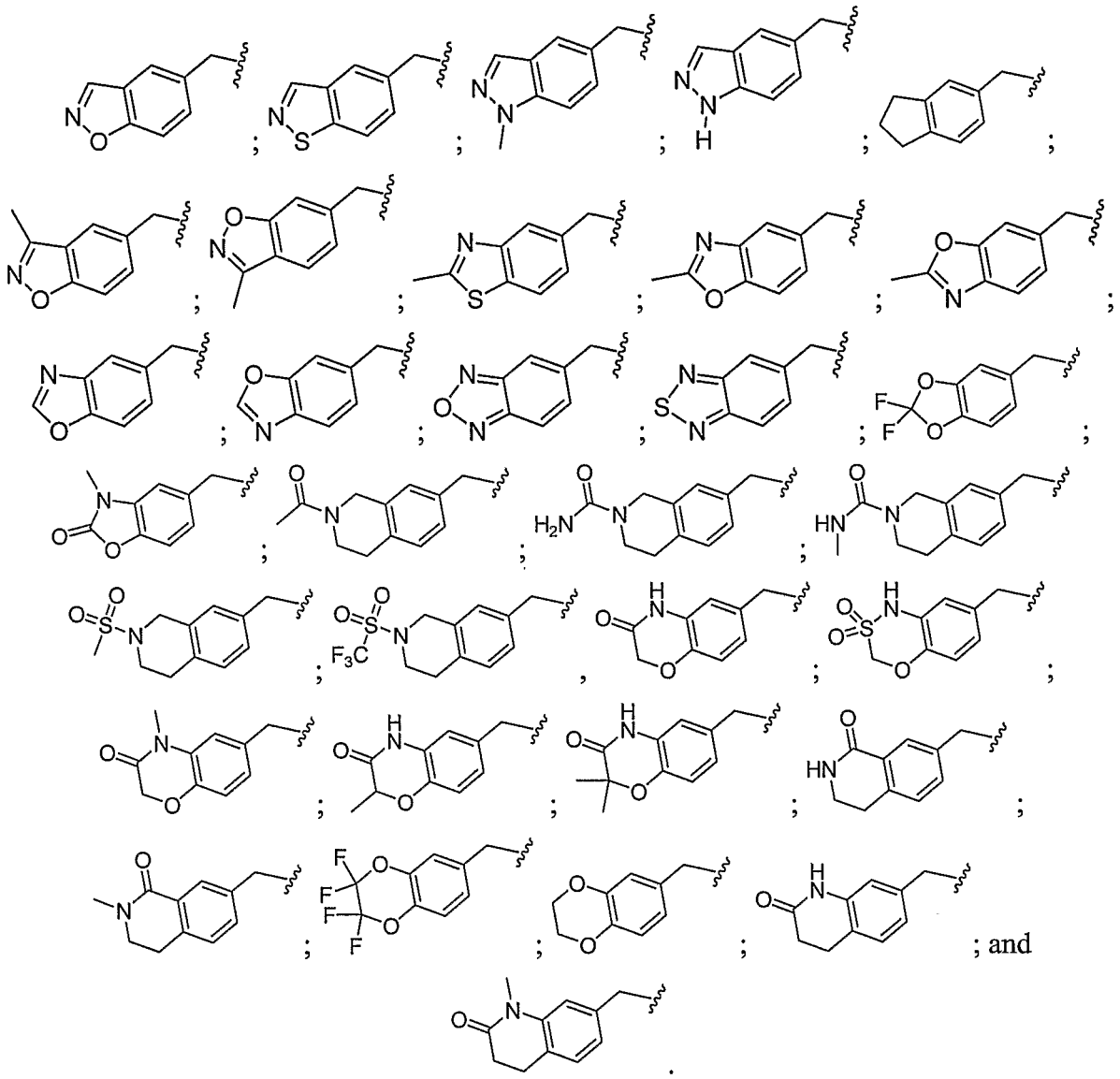


wherein all variables are as defined hereinabove.

For example, For example, in some embodiments, R^1 of the structures of Groups VI(a) and (b) may be selected from Substituent Group 8 as defined hereinabove.

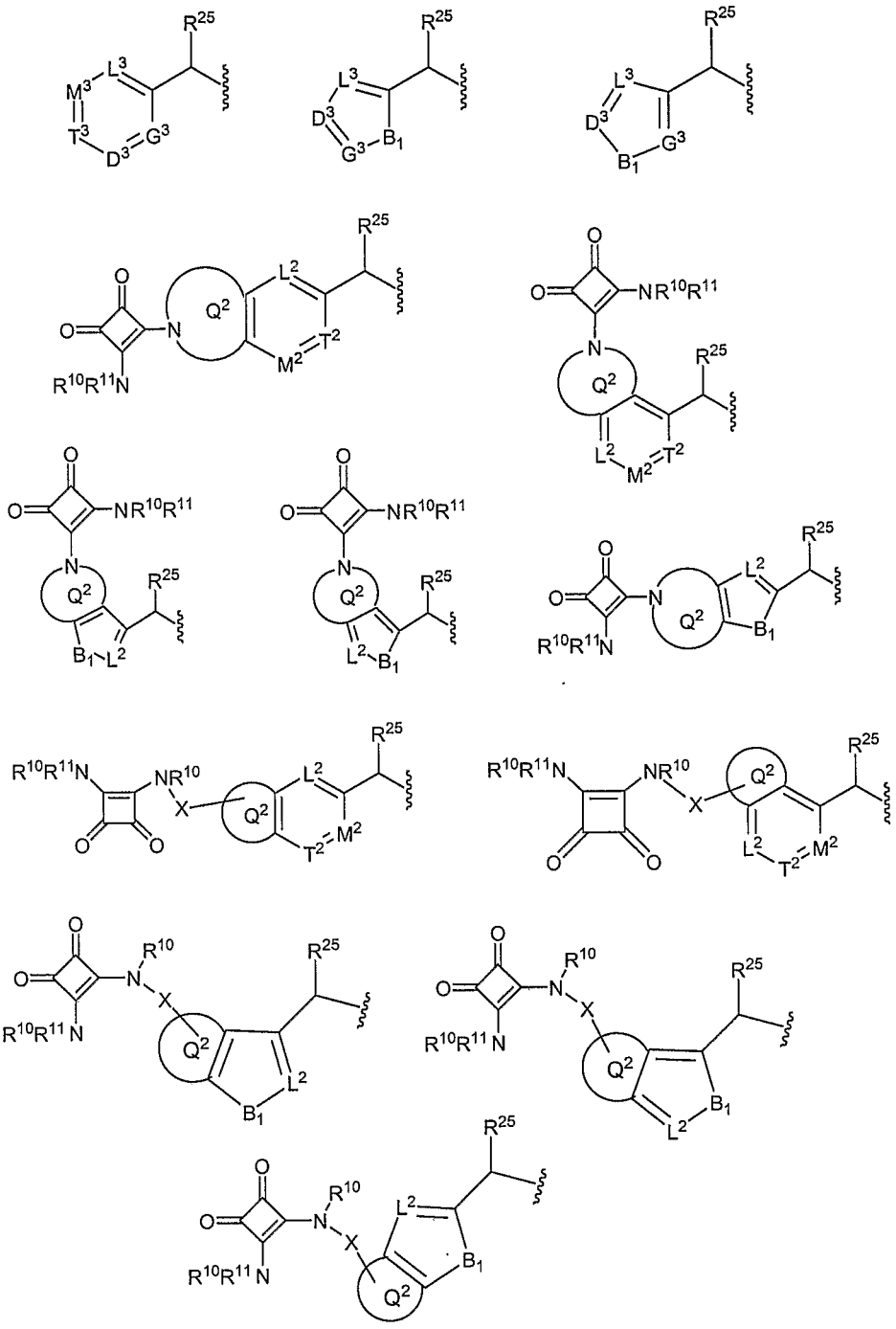
[0151] In still a further embodiment, R^1 of Formula (VI) may be selected from Substituent Group 9:





For example, in some embodiments, R^1 of the structures of Groups VI(a) and (b) may be selected from Substituent Group 9 as defined hereinabove.

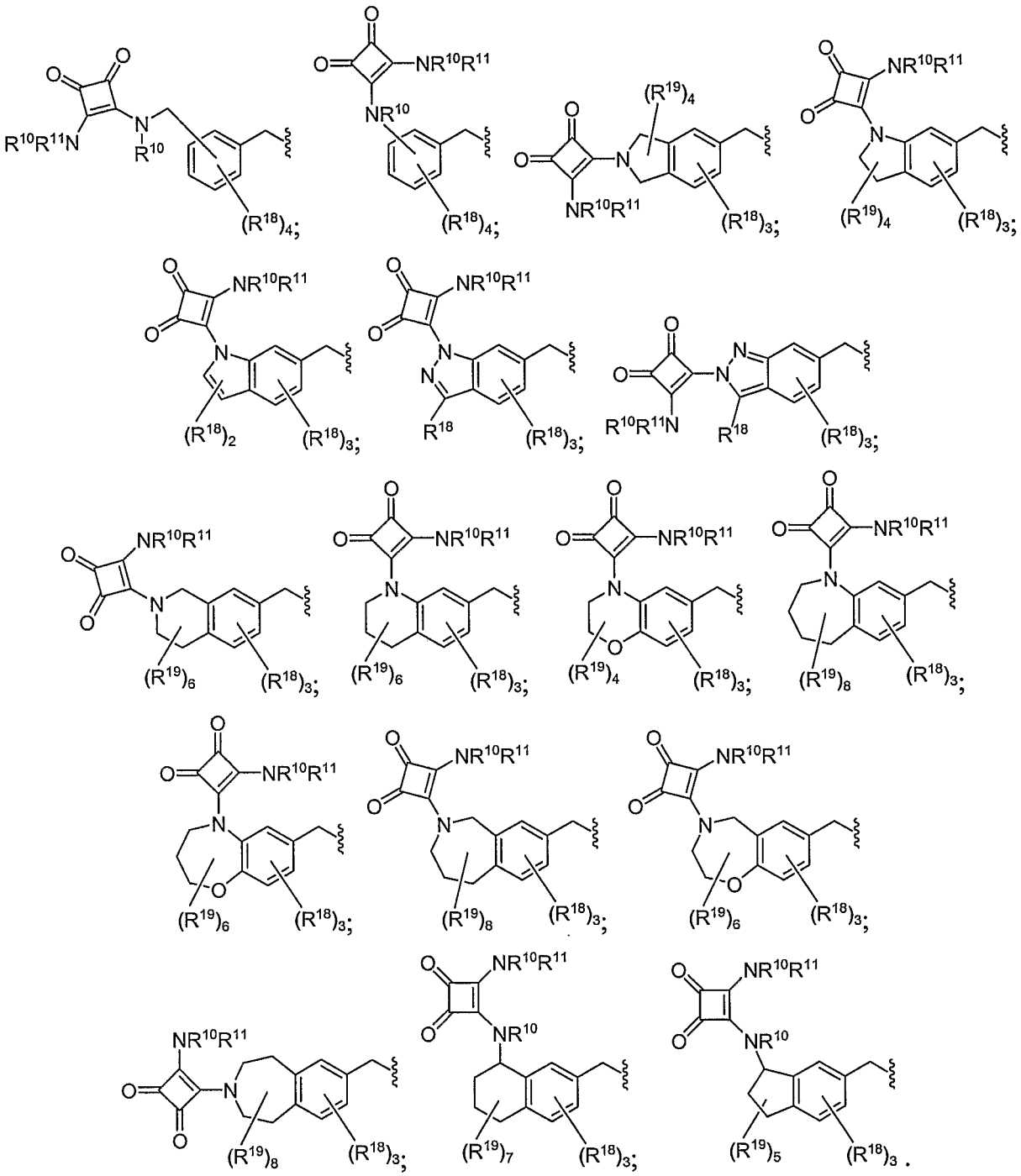
[0152] In one embodiment, R^1 of Formula (VI) may be selected from Substituent Group 10:



wherein all variables are as defined hereinabove.

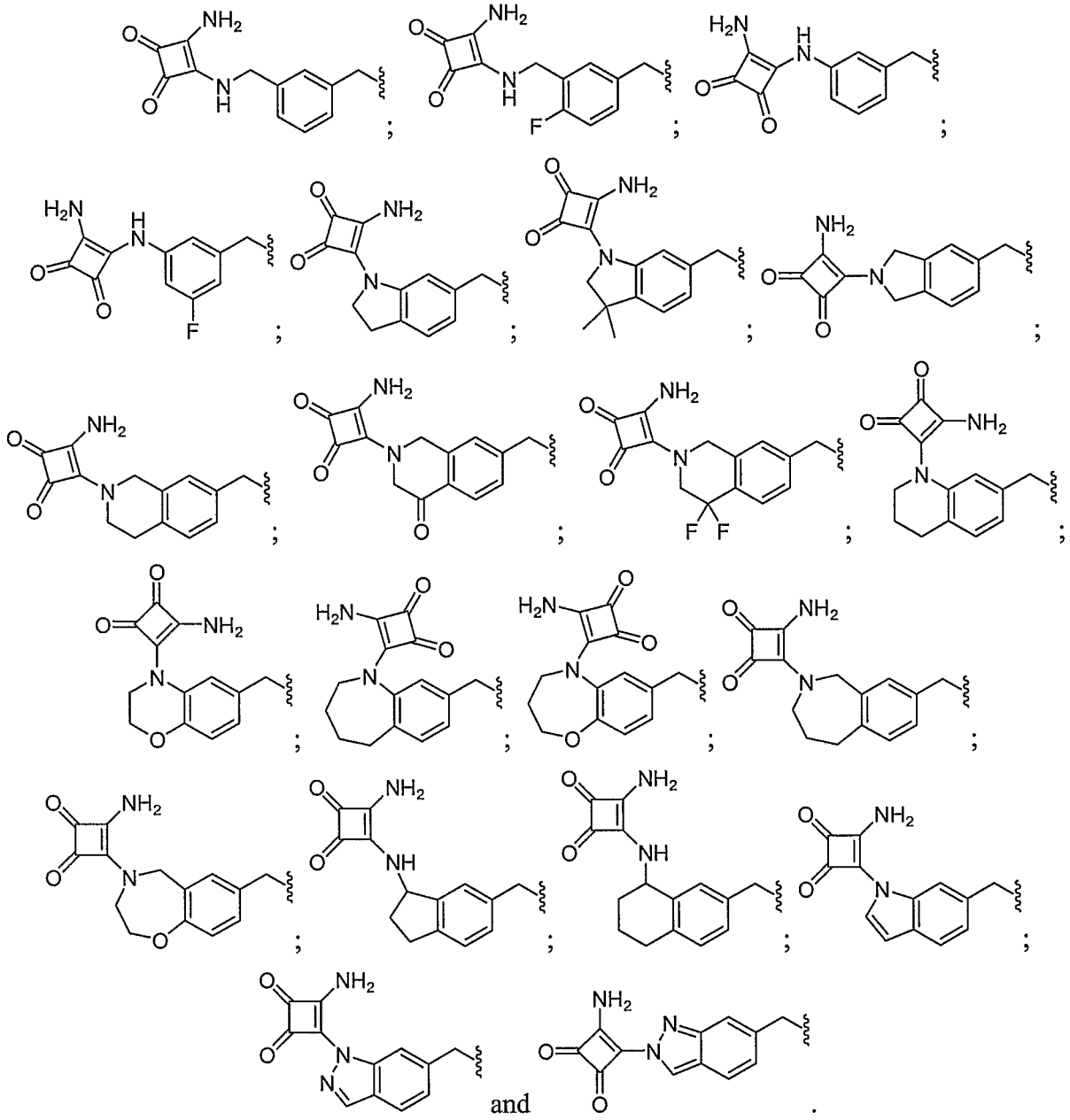
For example, in some embodiments, R^1 of the structures of Groups VI(a) and (b) may be selected from Substituent Group 10 as defined hereinabove.

[0153] In another embodiment, R^1 of Formula (VI) may be selected from Substituent Group 11:



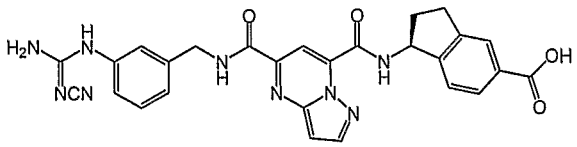
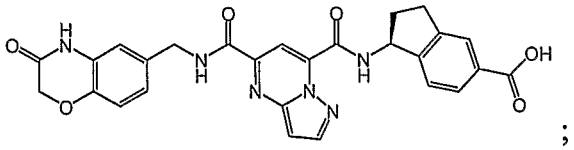
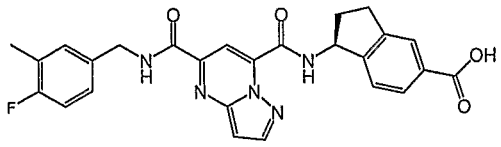
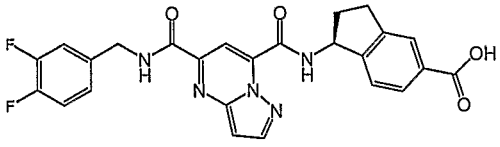
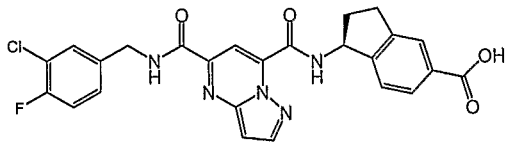
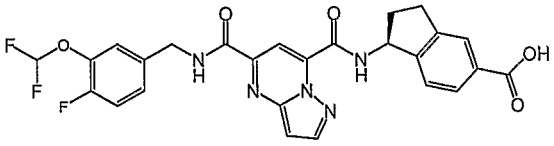
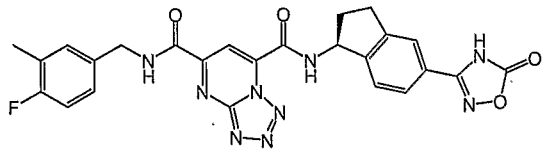
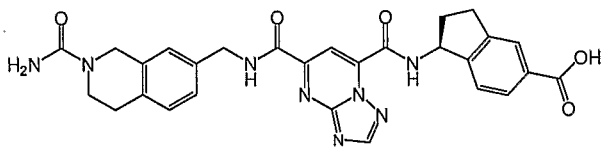
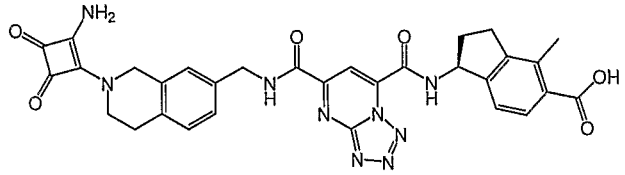
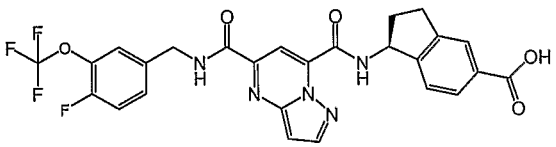
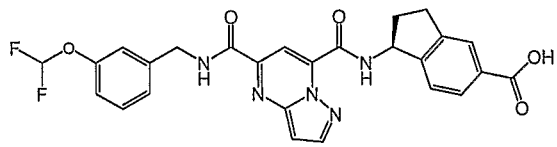
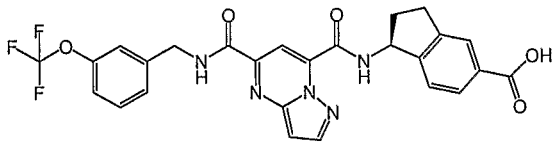
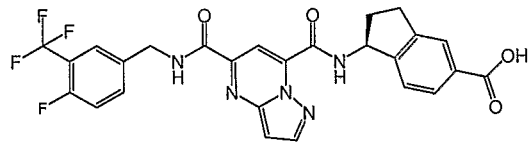
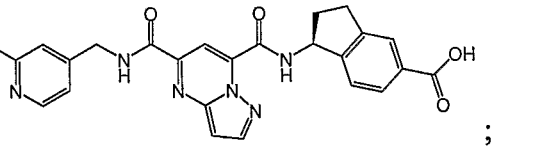
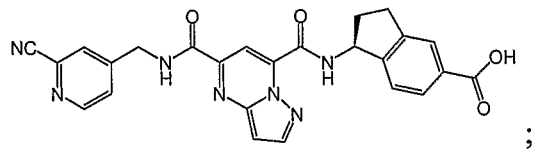
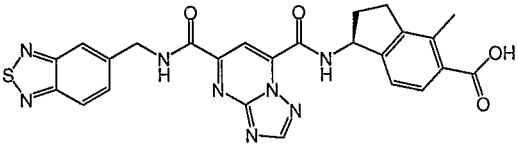
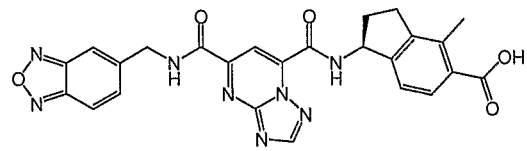
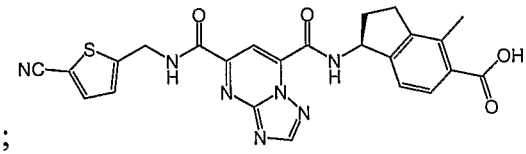
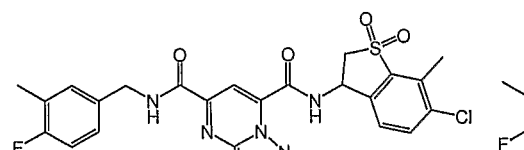
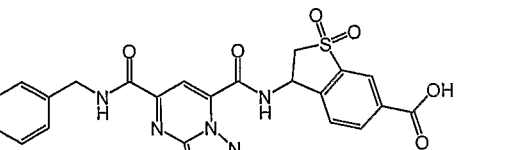
For example, in some embodiments, R^1 of the structures of Groups VI(a) and (b) may be selected from Substituent Group 11 as defined hereinabove.

[0154] In yet another embodiment, R^1 of Formula (VI) may be selected from Substituent Group 12:



For example, in some embodiments, R^1 of the structures of Groups VI(a) and (b) may be selected from Substituent Group 12 as defined hereinabove.

[0155] In still another embodiment, the present invention provides a compound selected from:

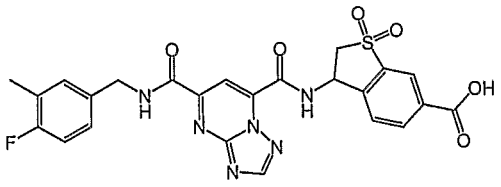
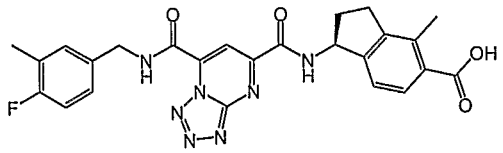
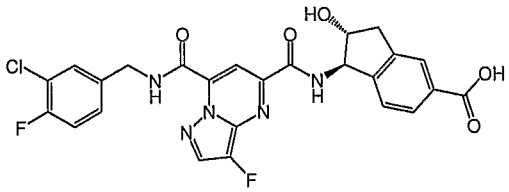
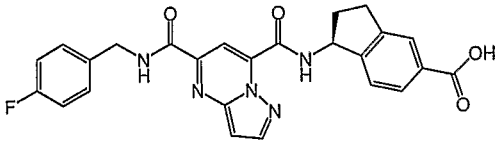
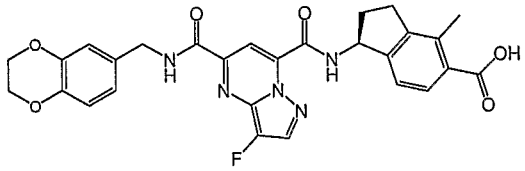
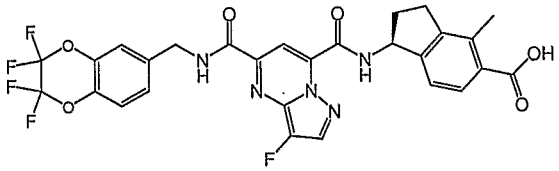
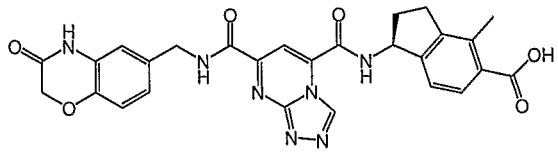
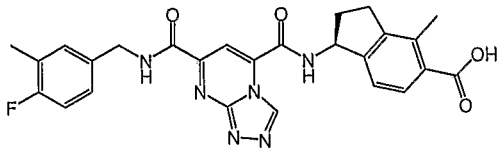
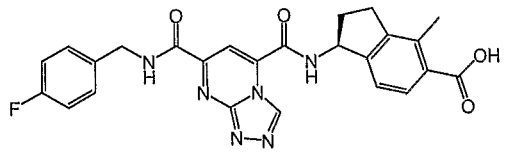
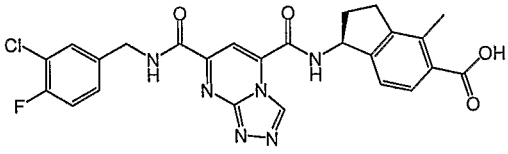
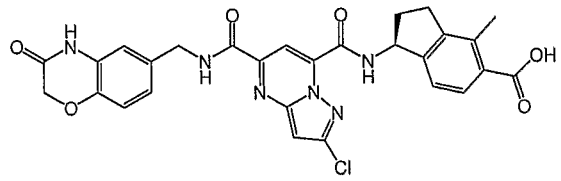
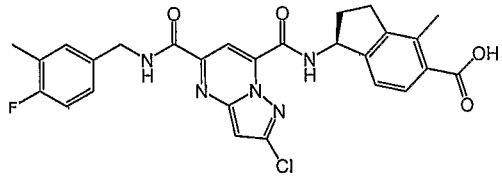
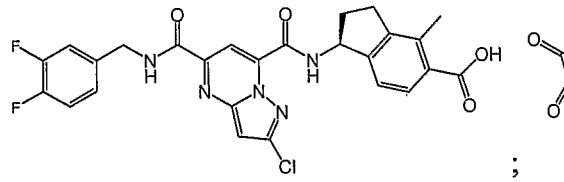
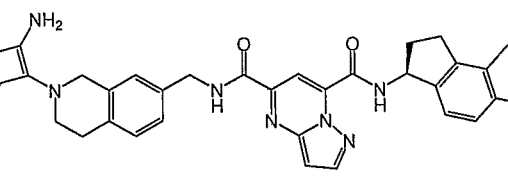
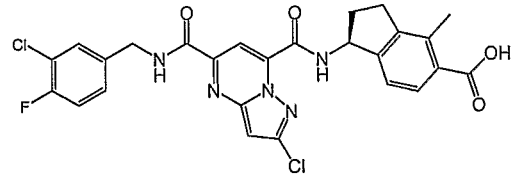

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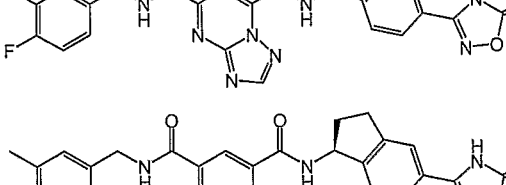
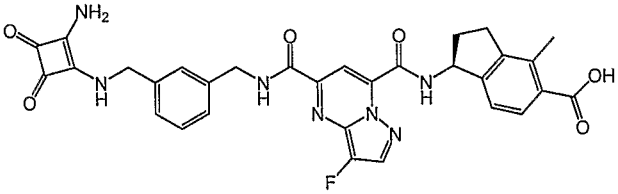
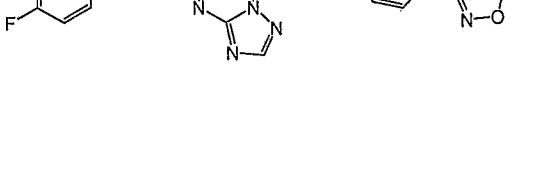
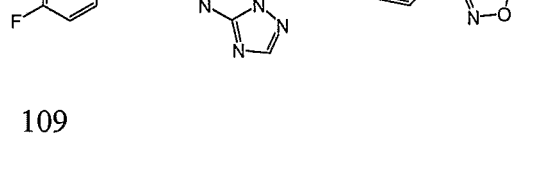
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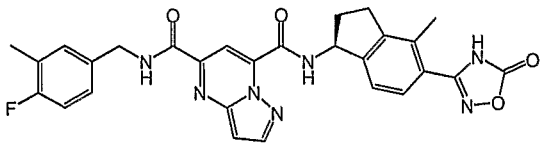
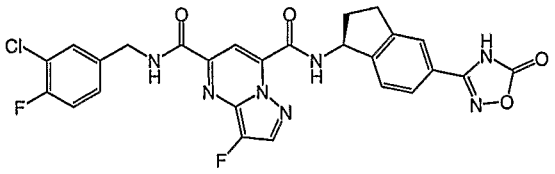
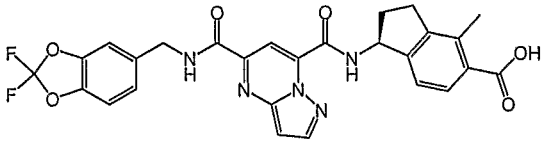
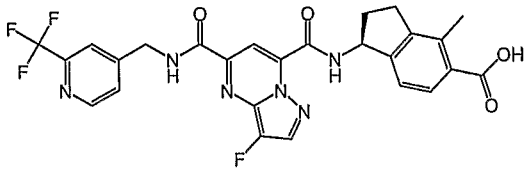
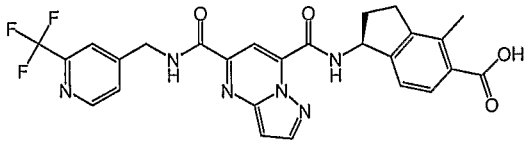
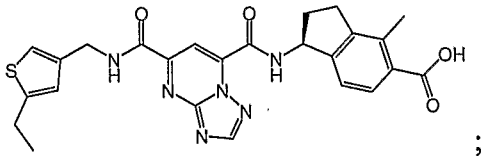
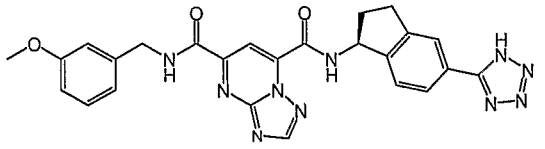
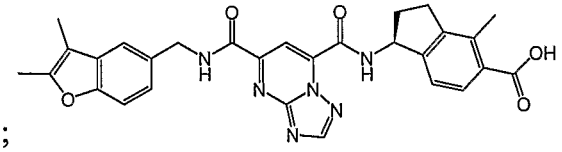
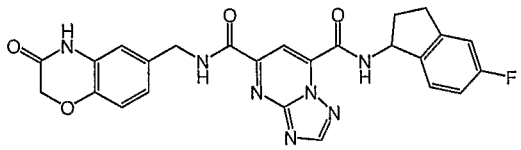
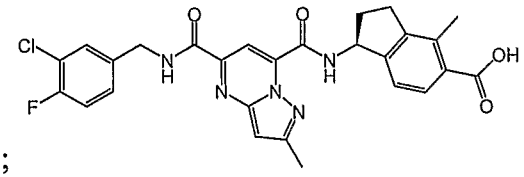
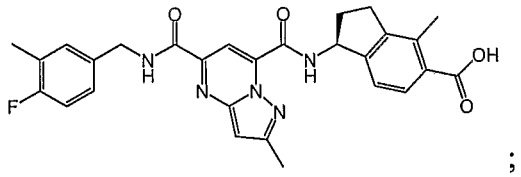
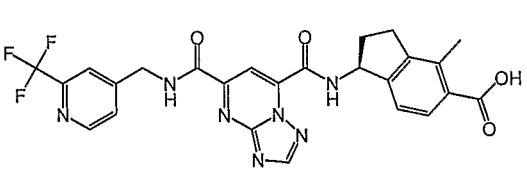
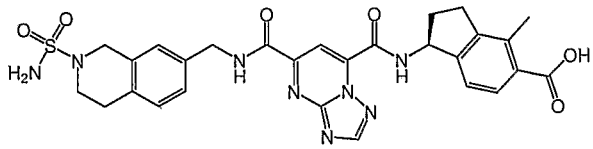
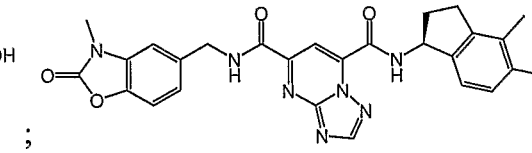
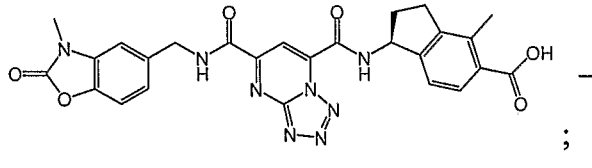
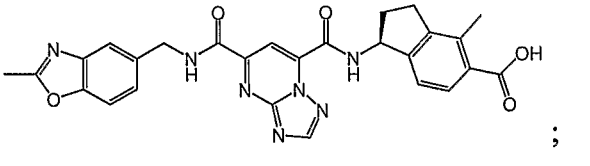
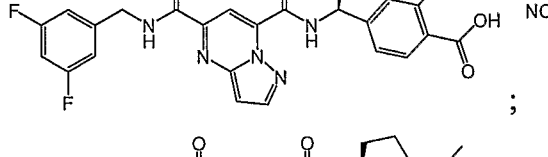
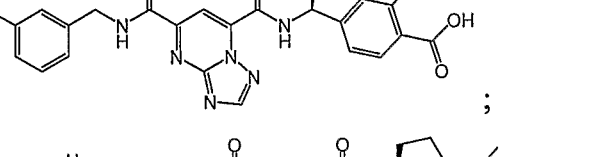
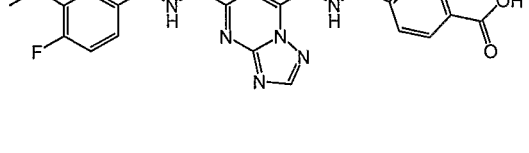
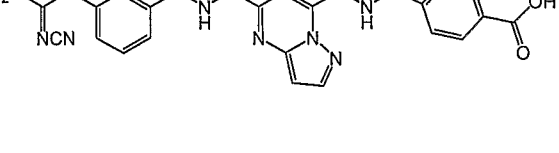
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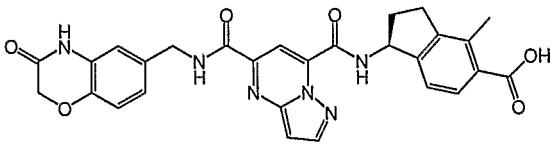
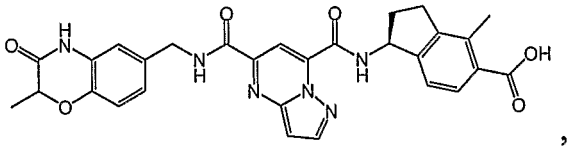
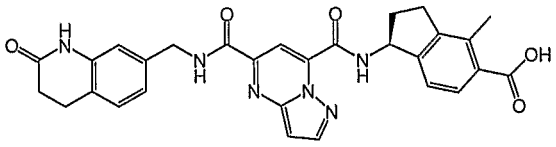
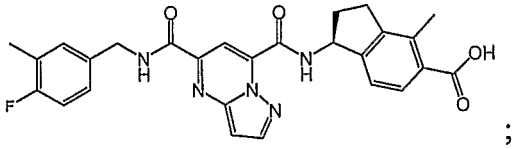
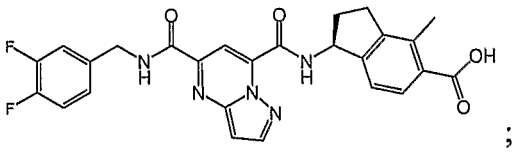
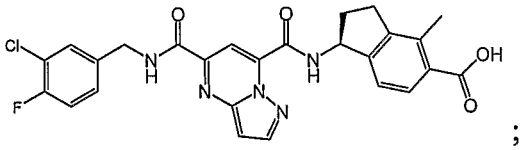
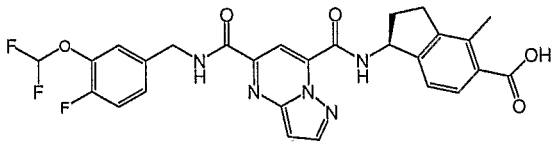
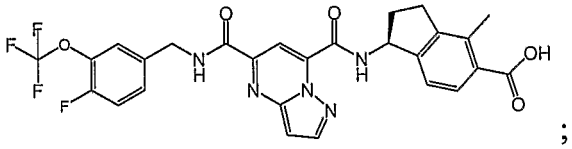
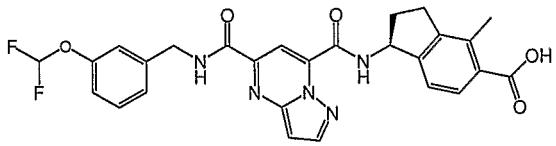
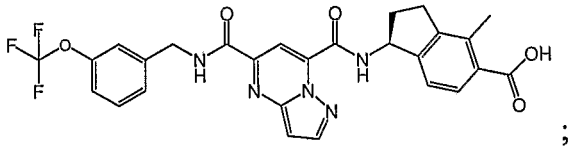
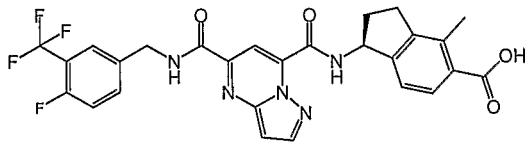
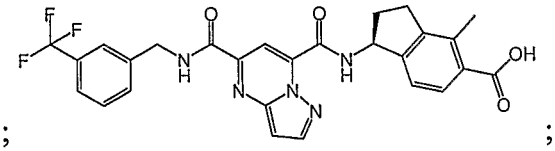
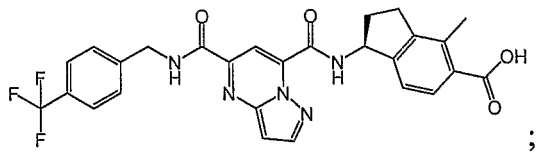
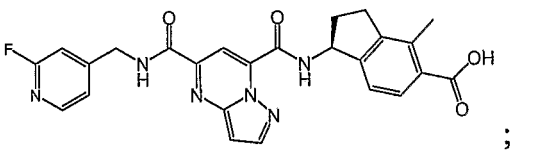
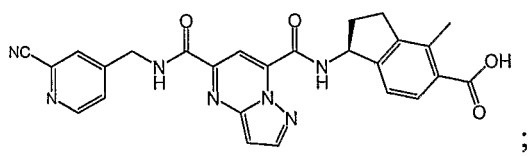
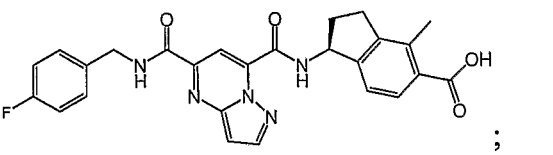
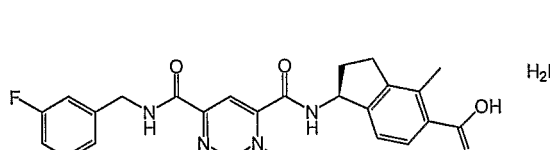
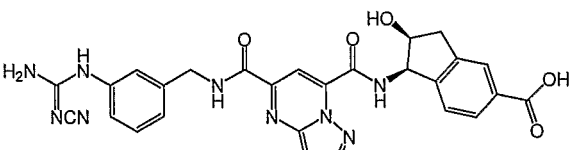
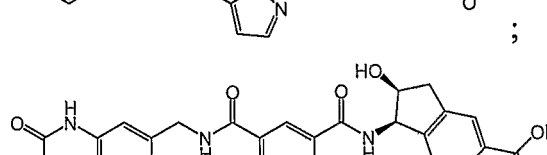
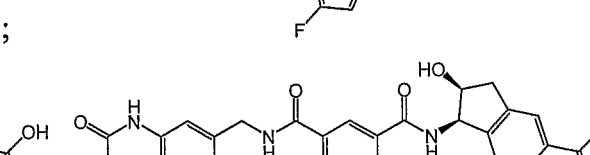
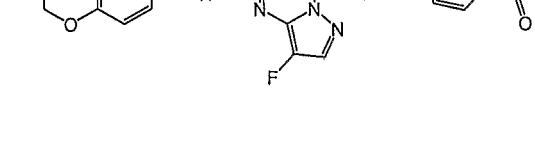
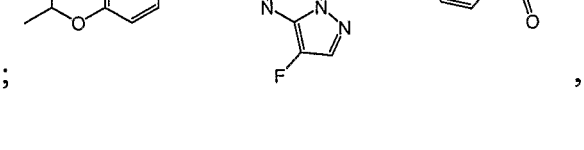
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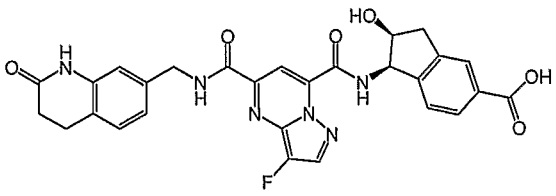
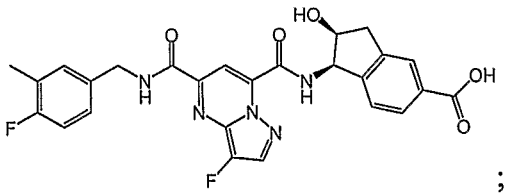
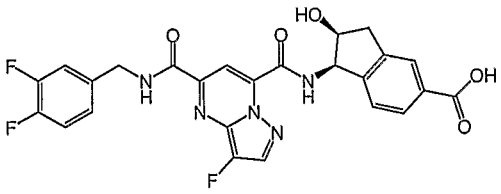
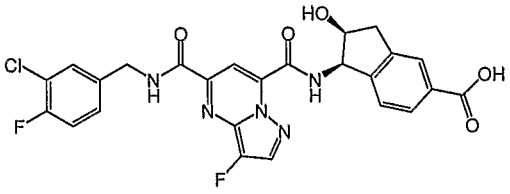
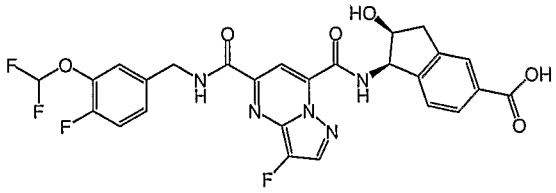
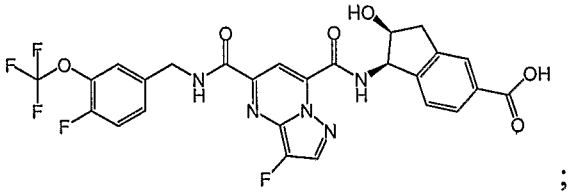
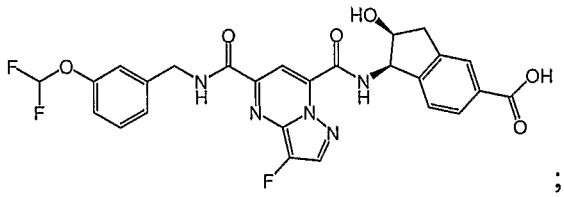
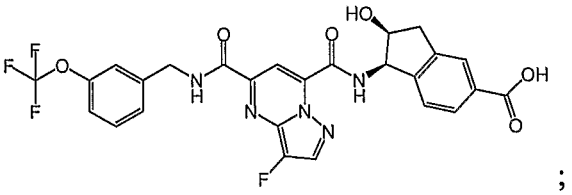
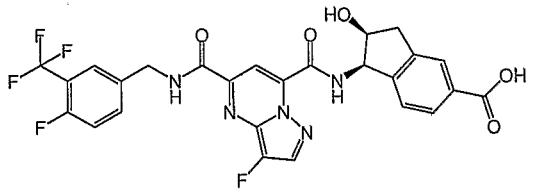
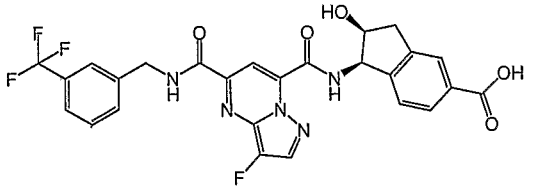
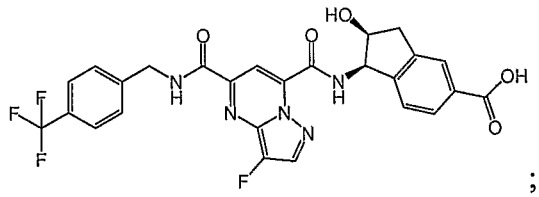
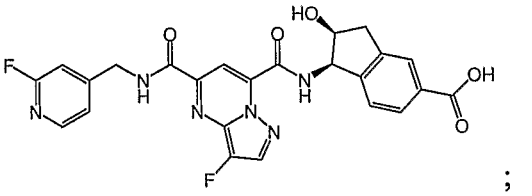
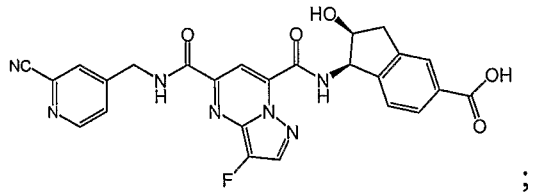
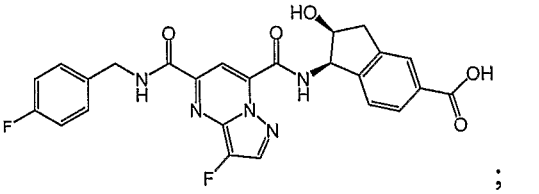
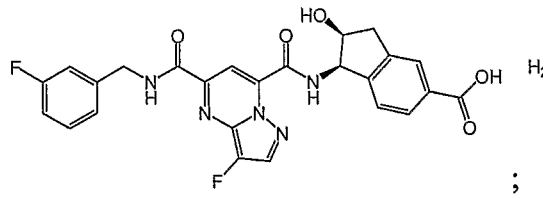
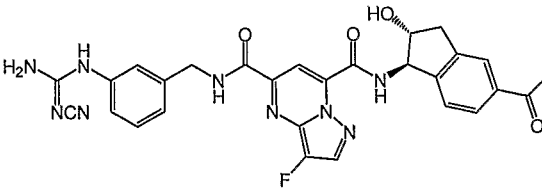
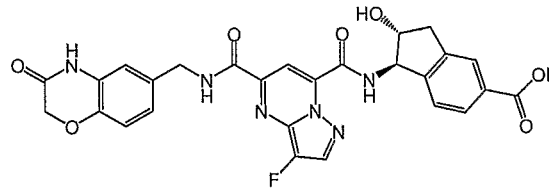
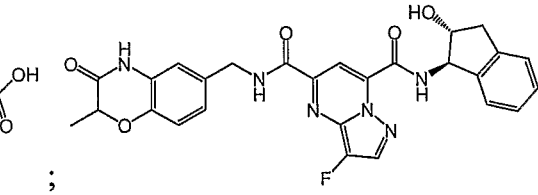
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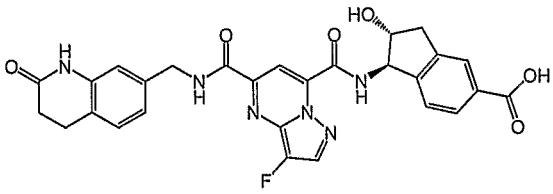
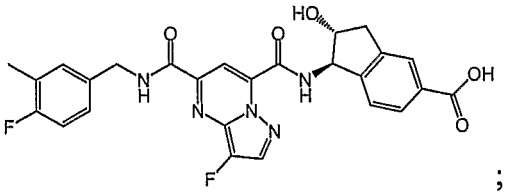
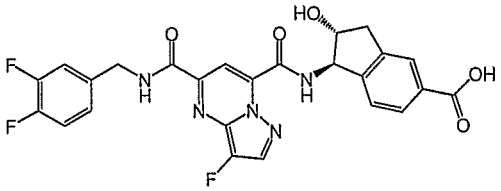
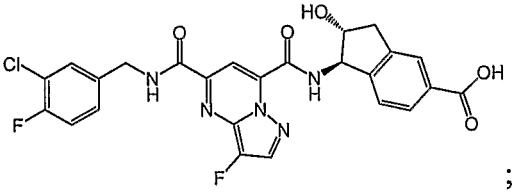
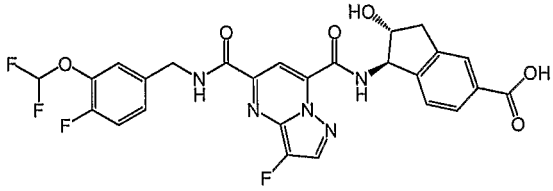
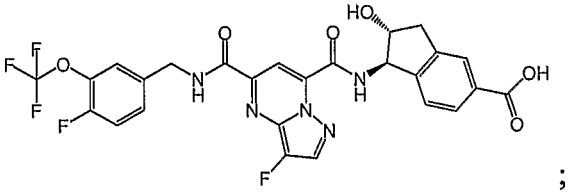
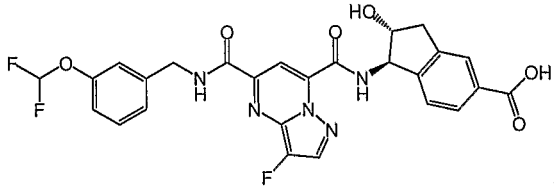
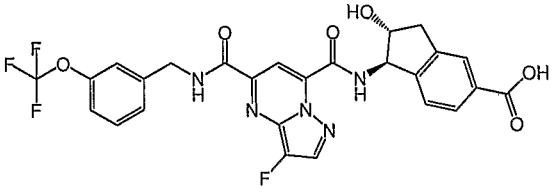
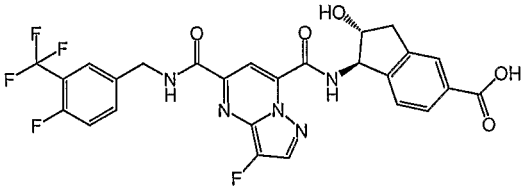
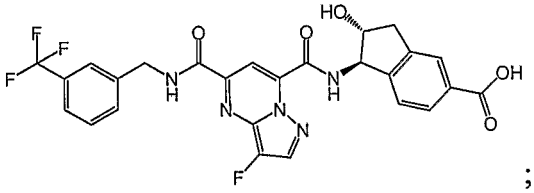
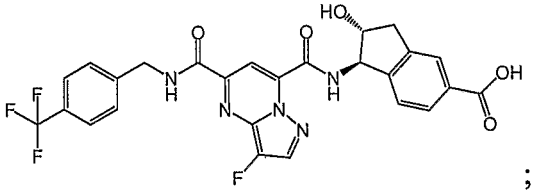
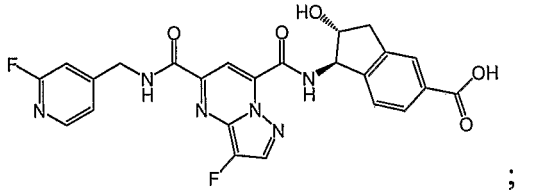
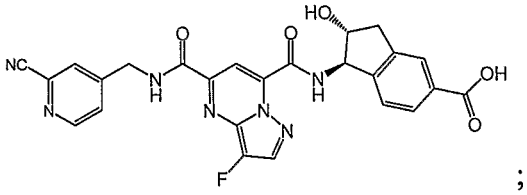
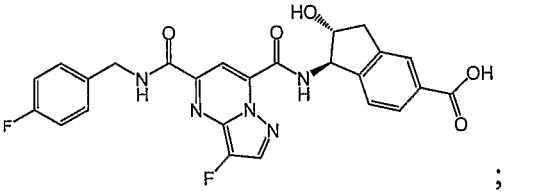
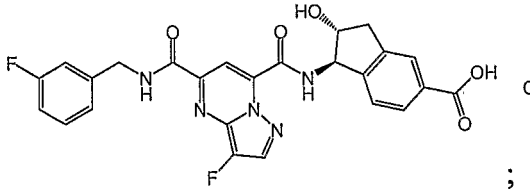
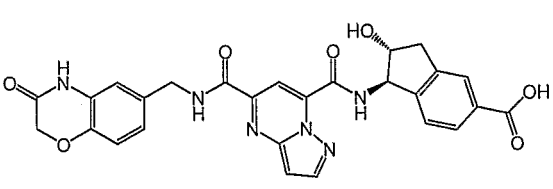
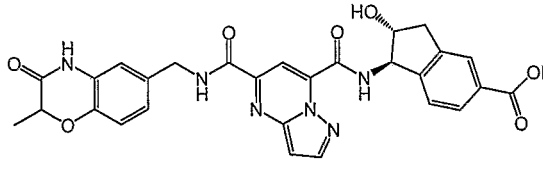
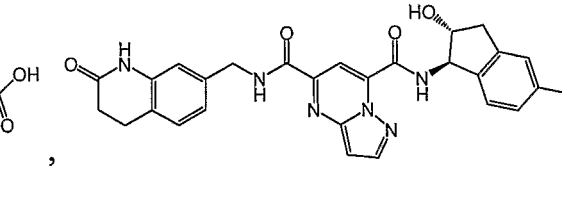
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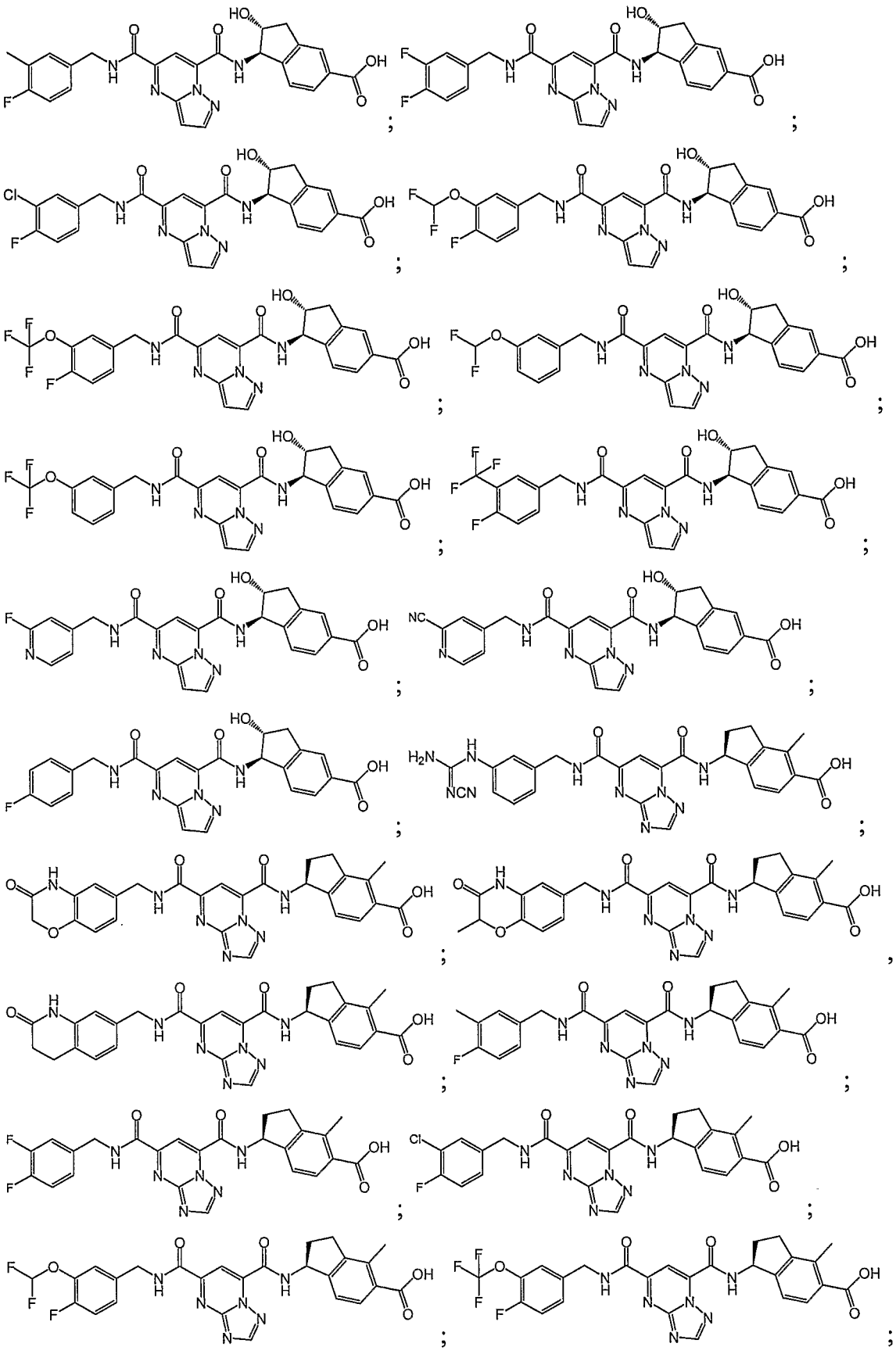
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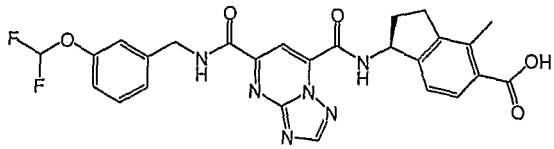
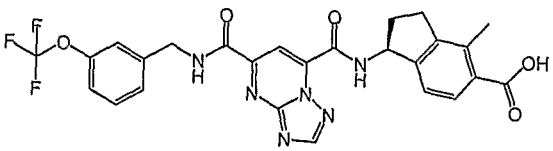
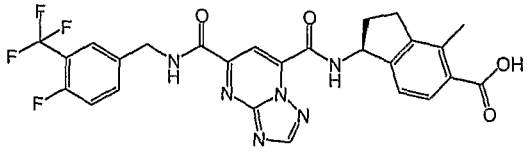
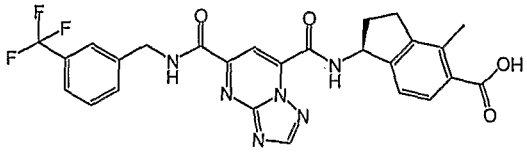
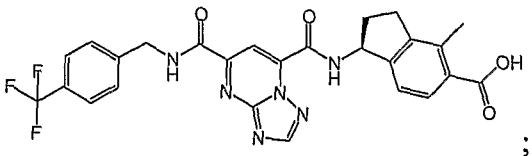
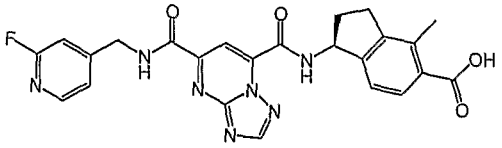
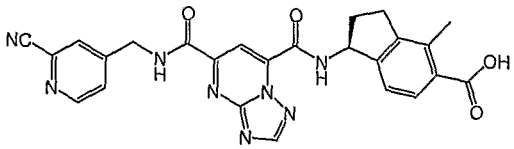
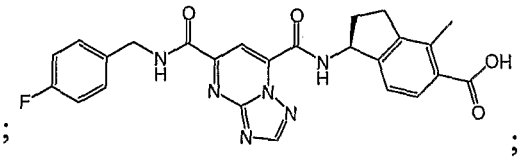
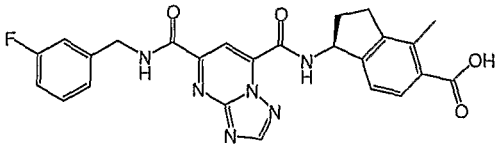
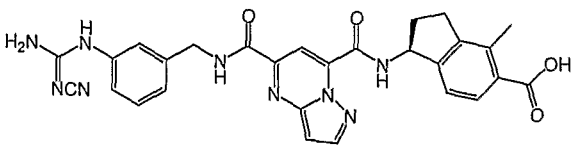
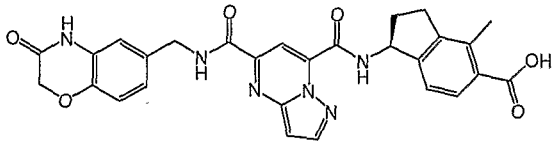
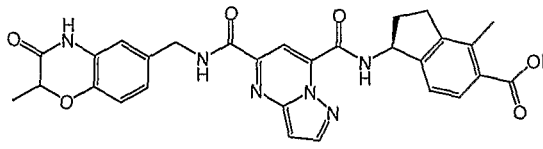
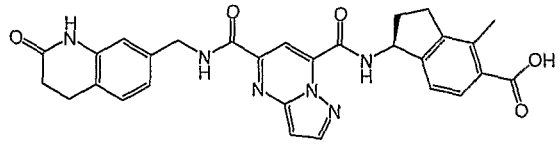
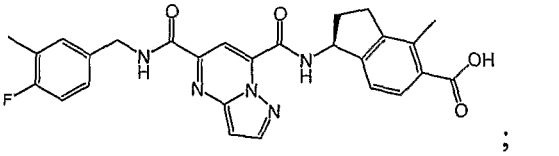
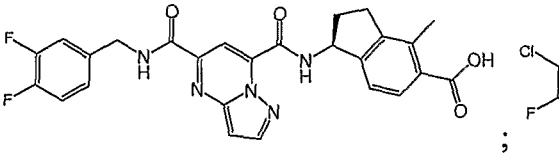
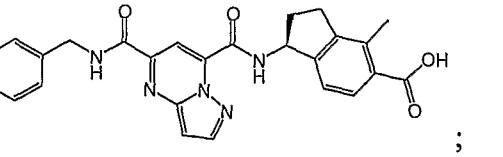
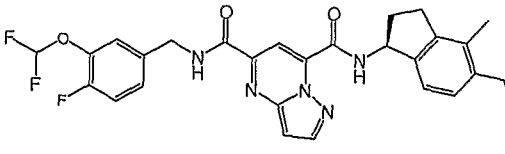
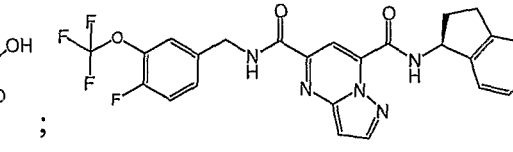
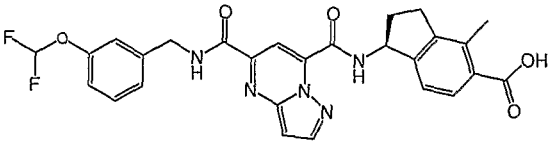
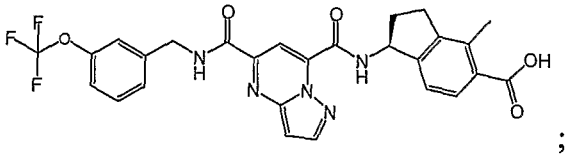
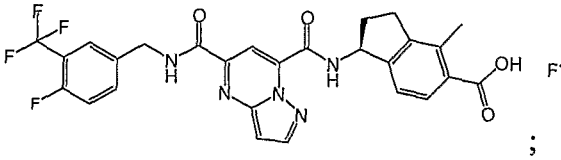
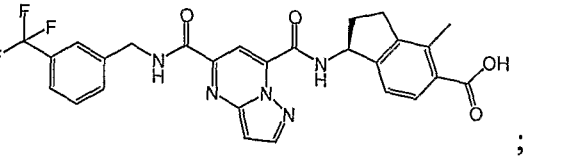
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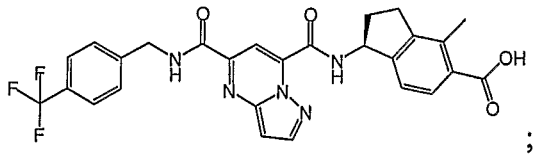
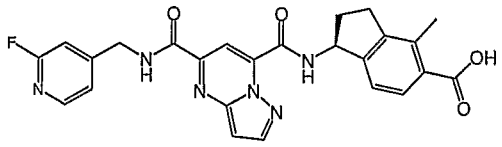
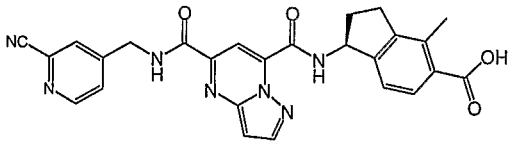
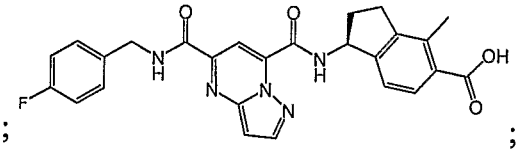
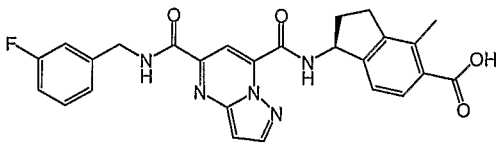
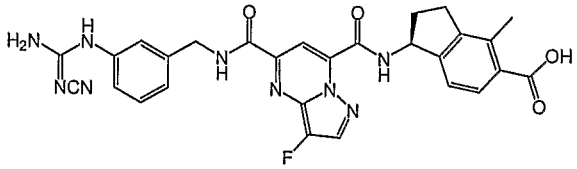
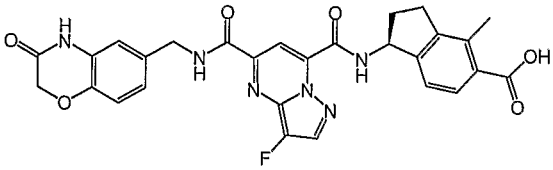
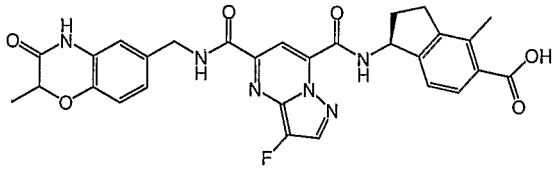
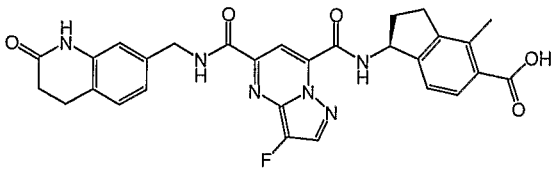
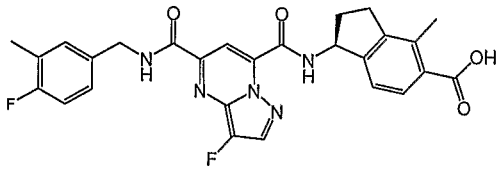
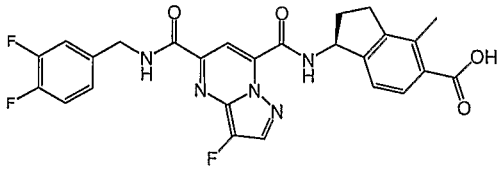
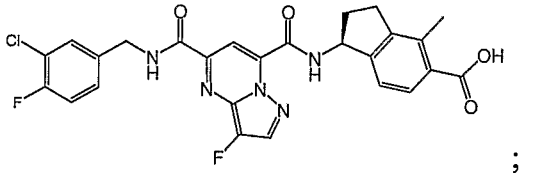
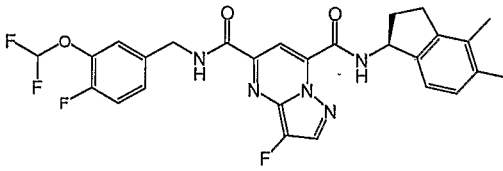
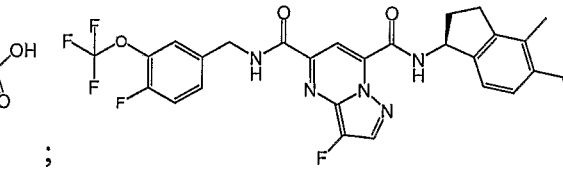
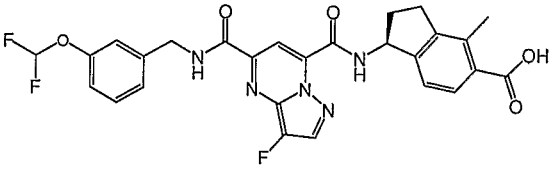
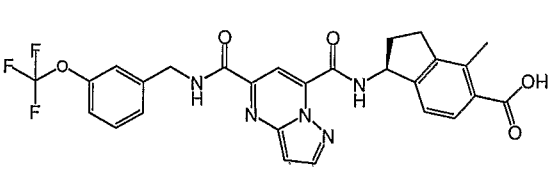
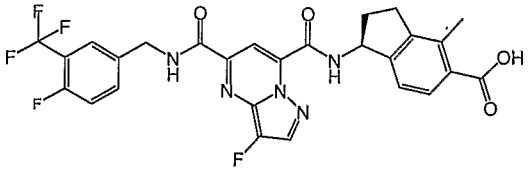
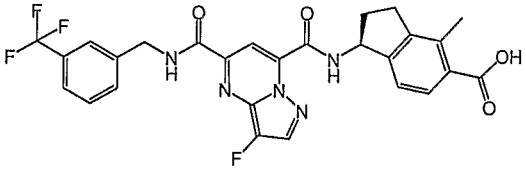
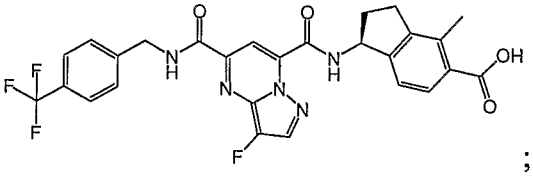
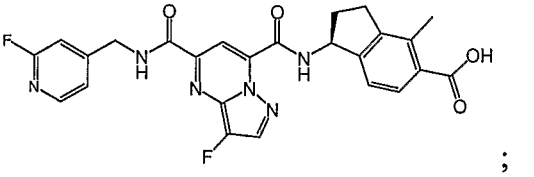
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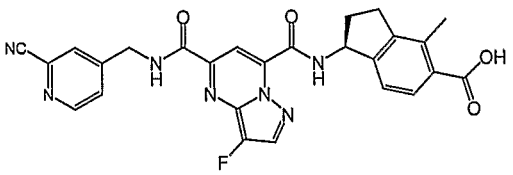
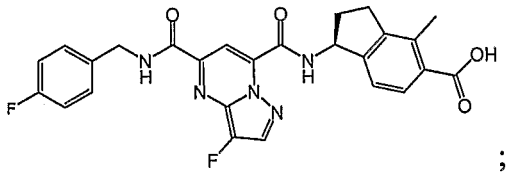
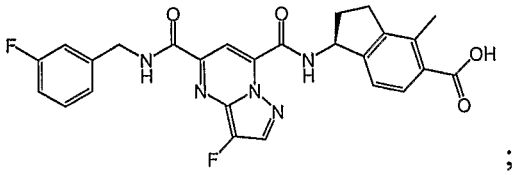
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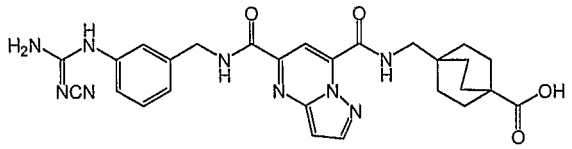
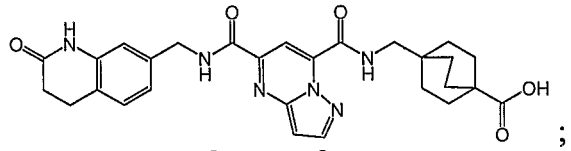
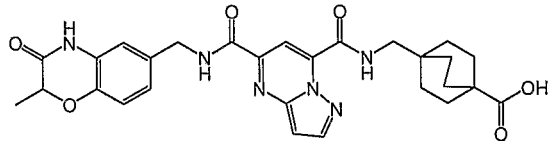
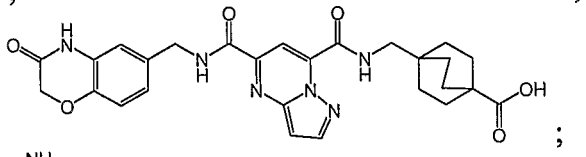
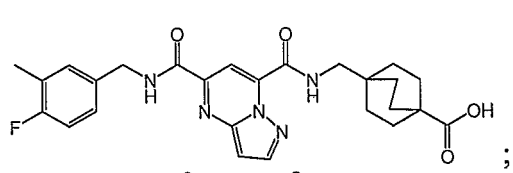
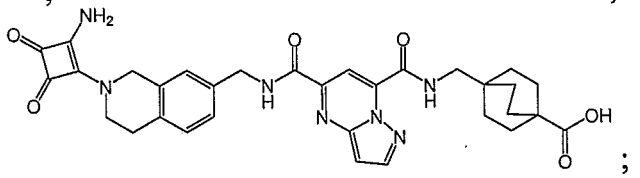
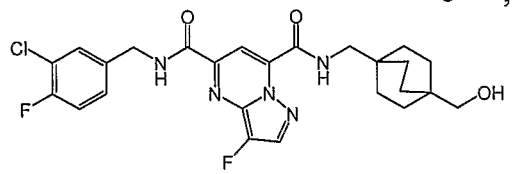
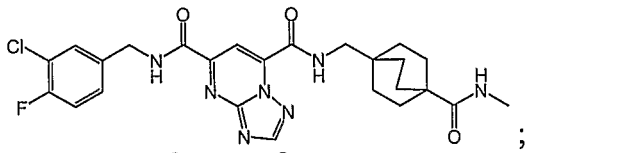
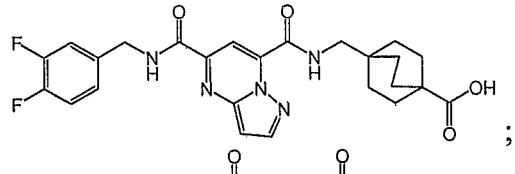
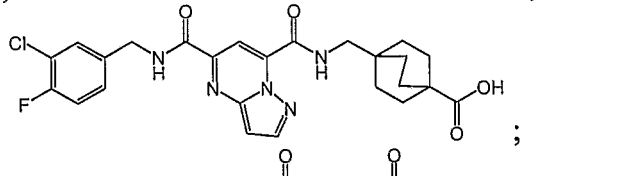
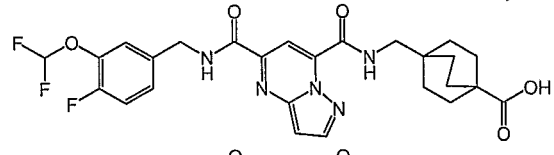
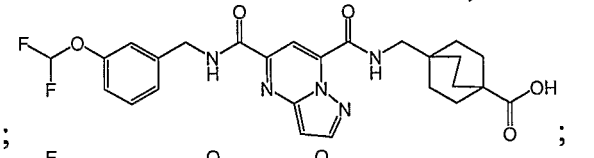
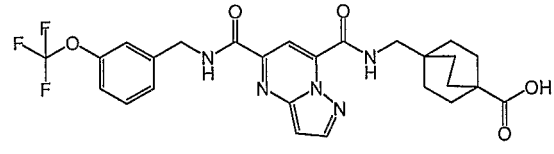
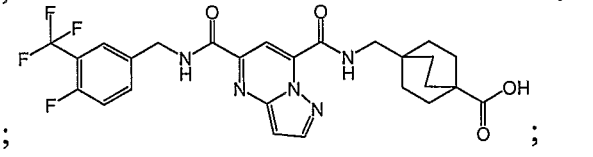
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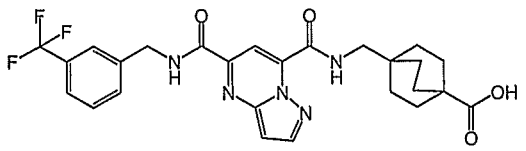
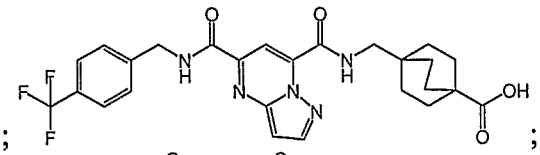
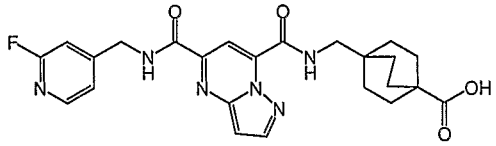
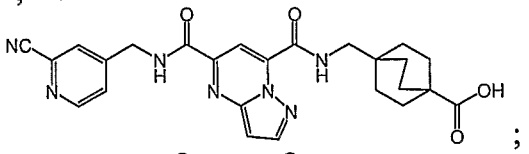
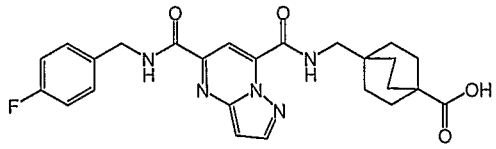
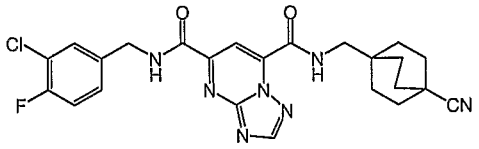
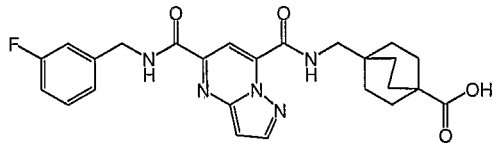
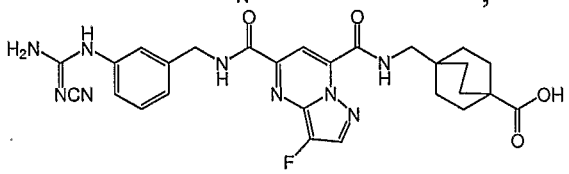
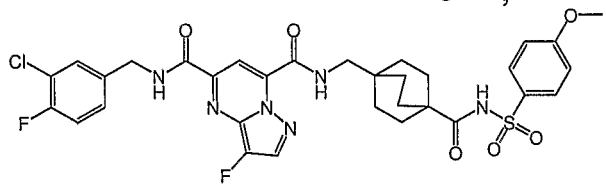
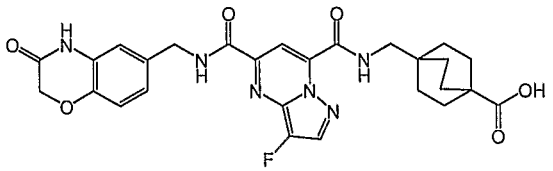
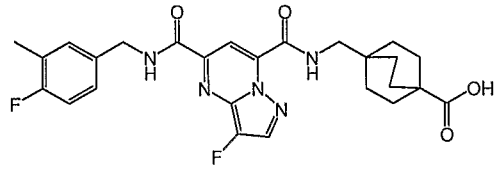
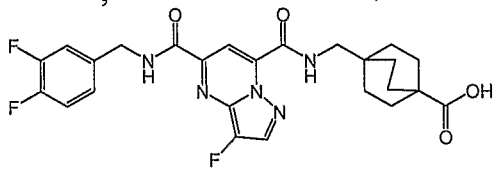
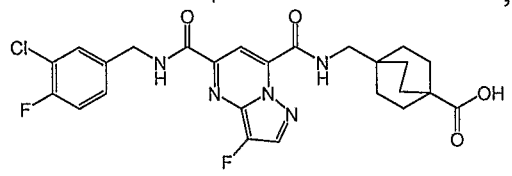
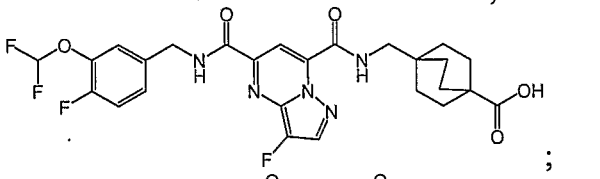
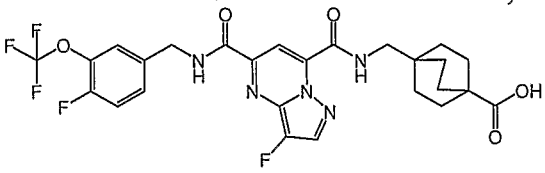
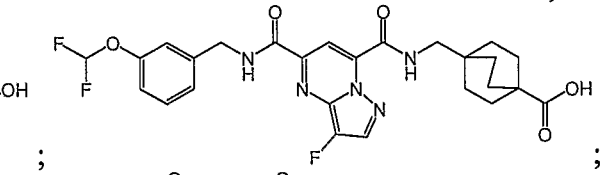
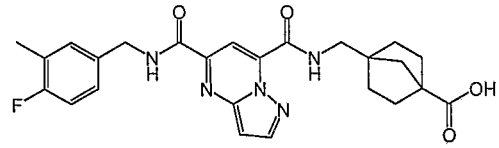
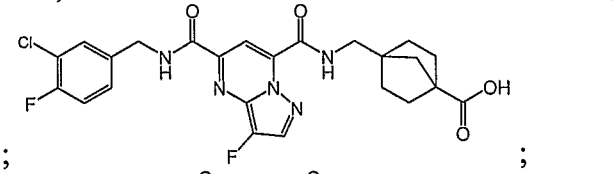
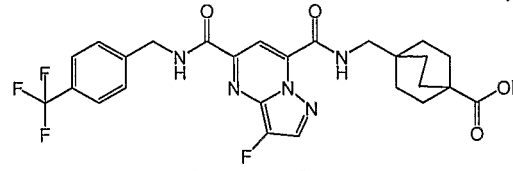
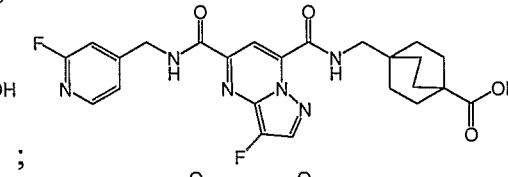
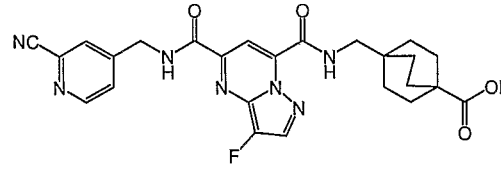
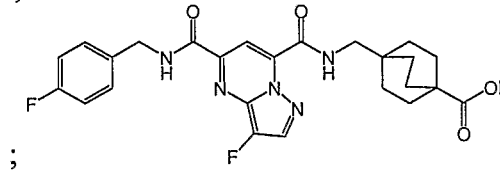
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or a pharmaceutically acceptable salt thereof.

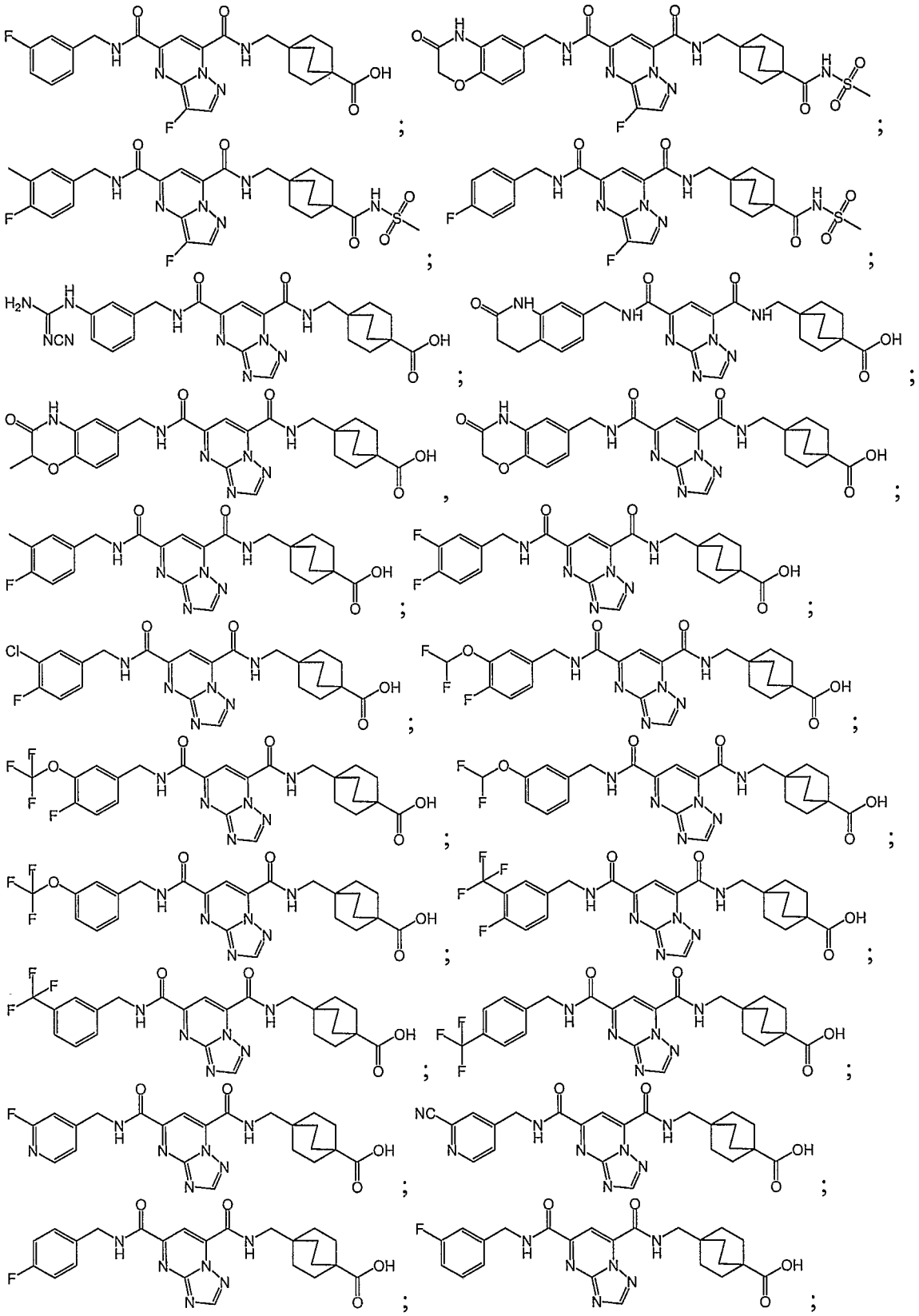
[0156] In a further embodiment, the present invention provides a compound selected from:


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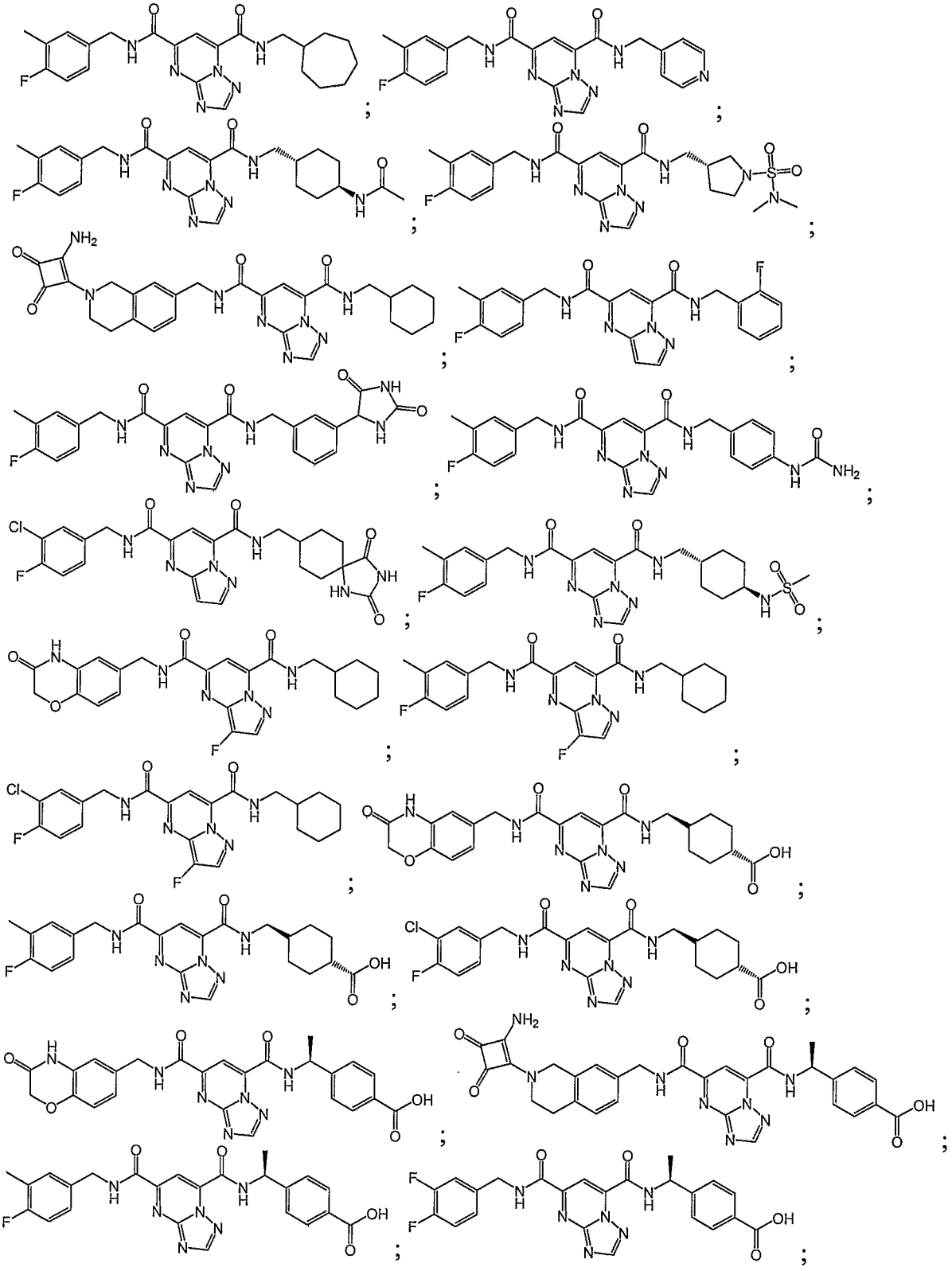
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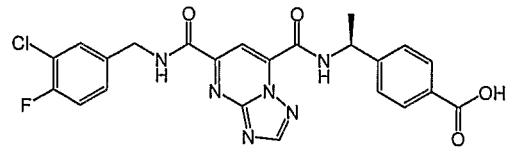
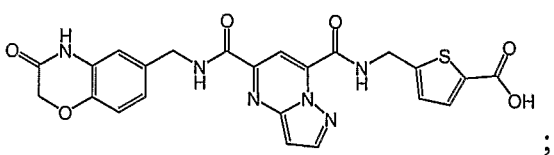
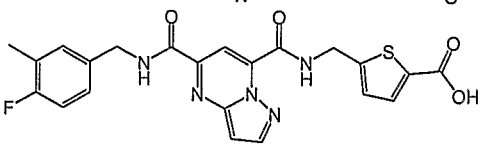
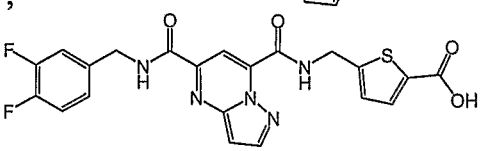
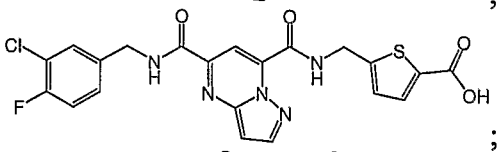
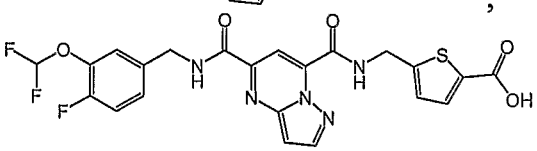
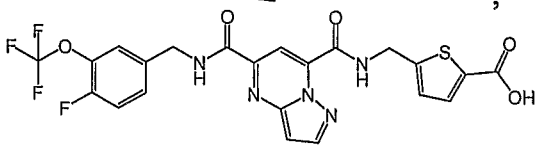
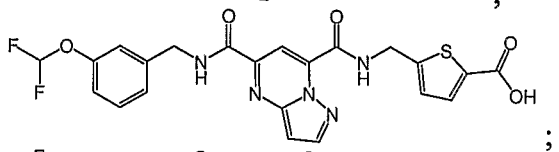
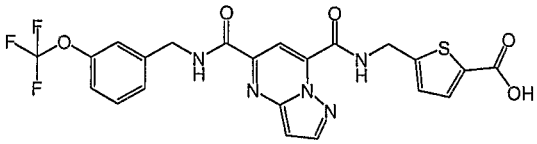
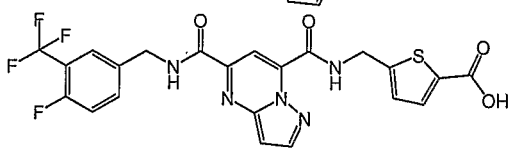
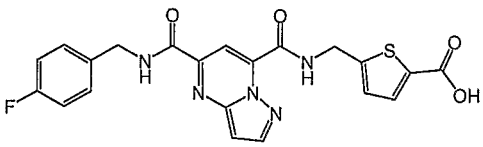
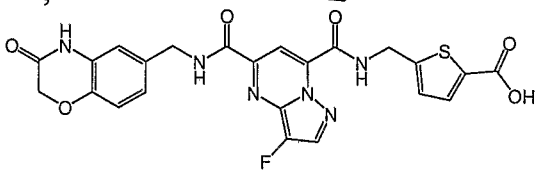
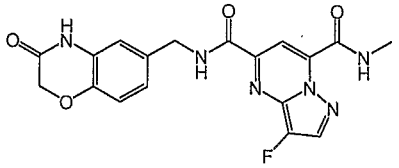
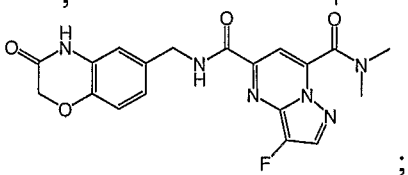
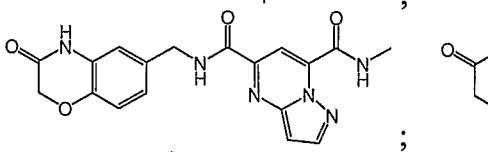
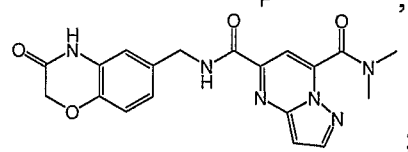
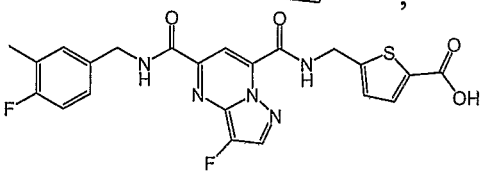
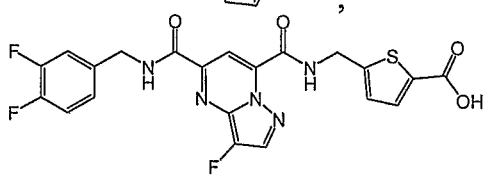
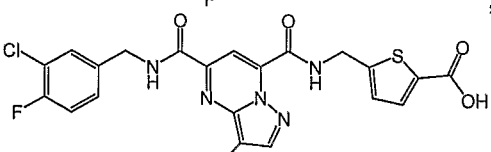
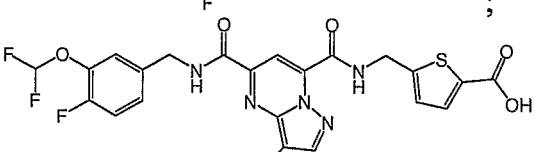
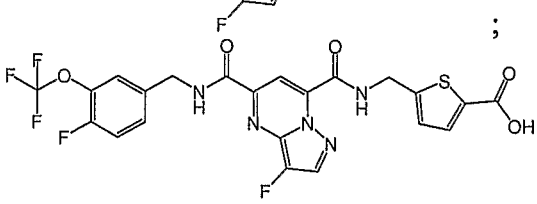
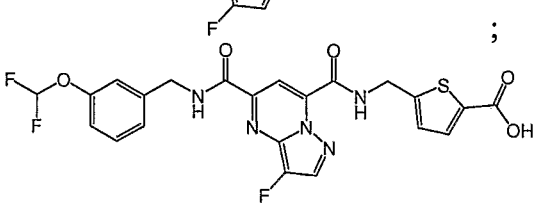
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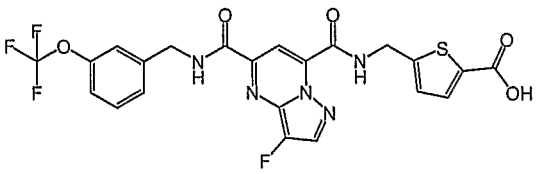
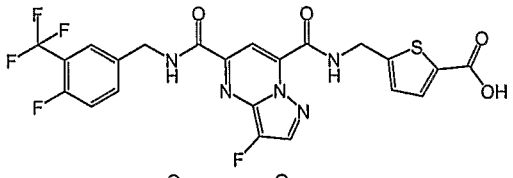
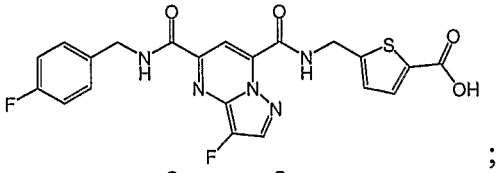
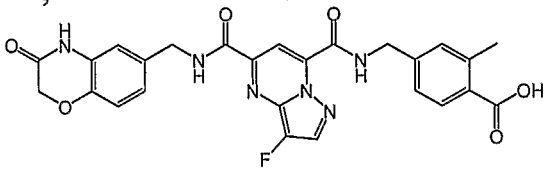
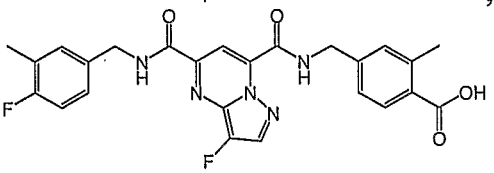
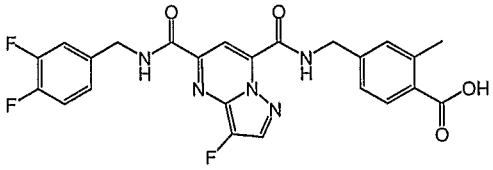
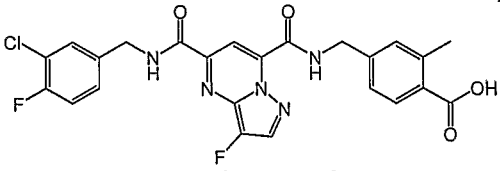
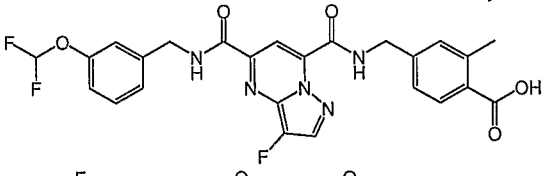
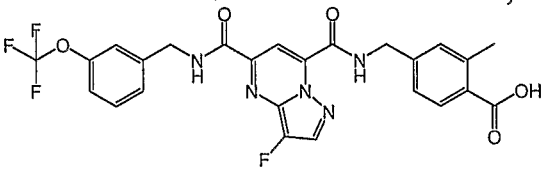
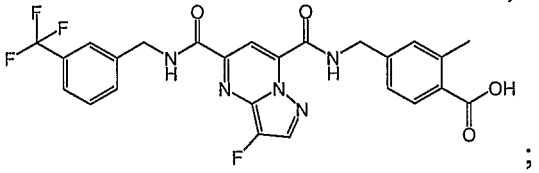
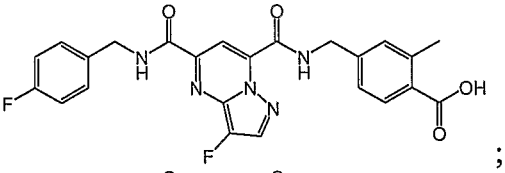
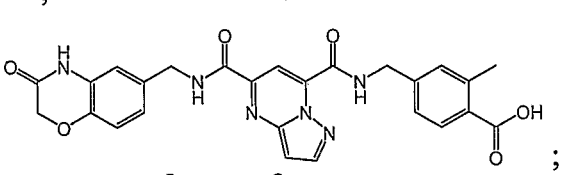
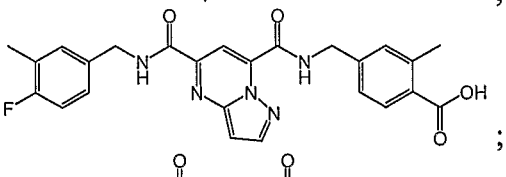
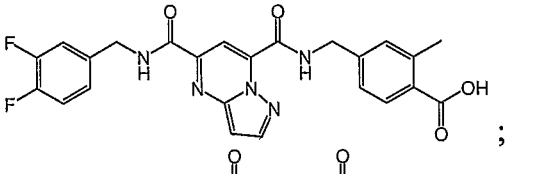
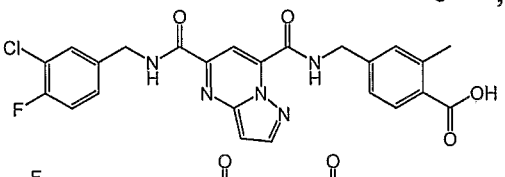
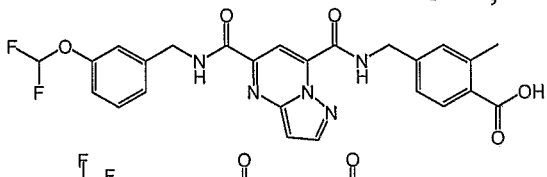
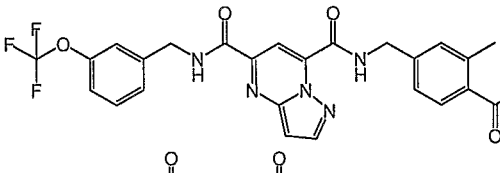
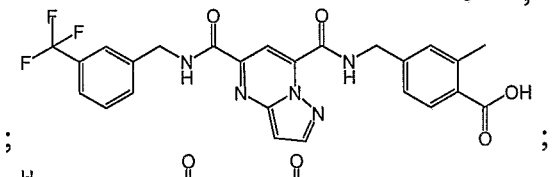
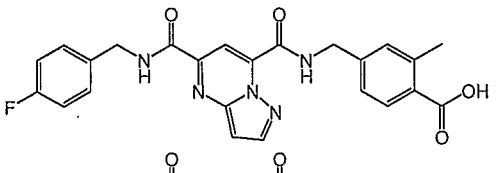
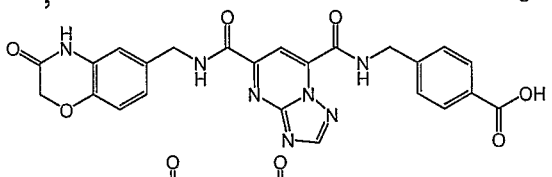
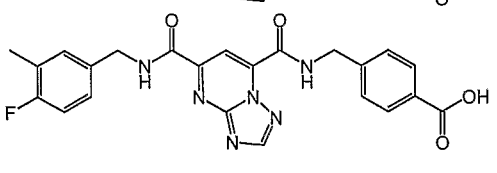
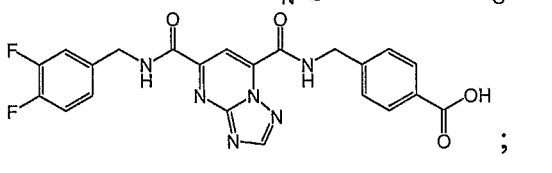


or a pharmaceutically acceptable salt thereof.

[0157] In yet a further embodiment, the present invention provides a compound selected from:

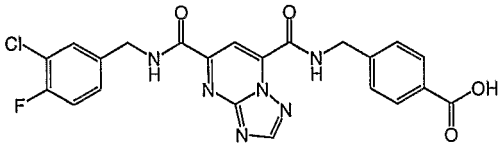
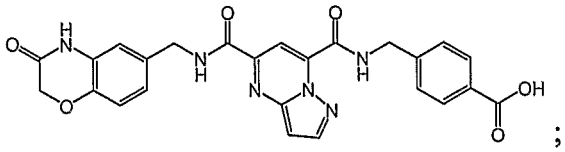
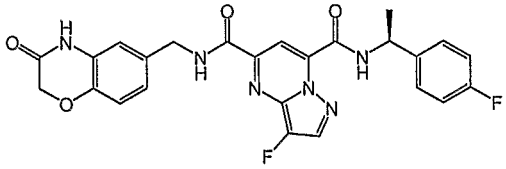
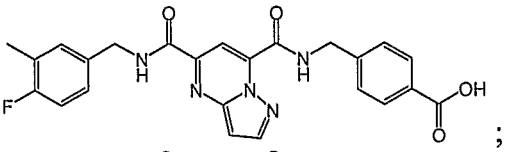
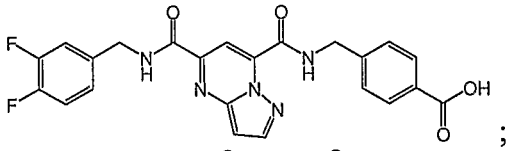
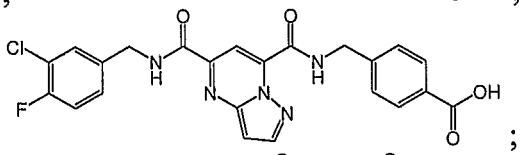
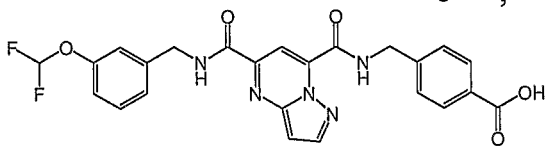
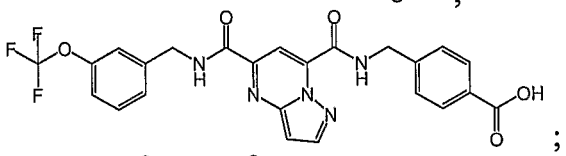
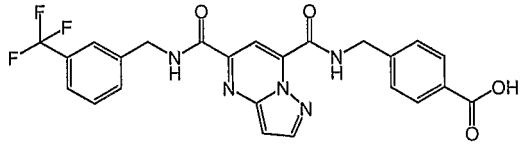
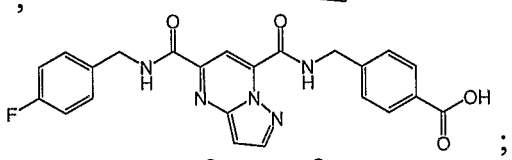
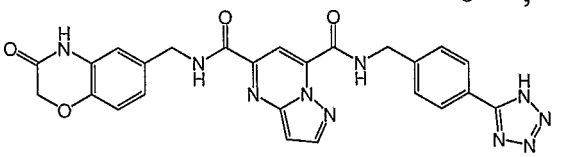
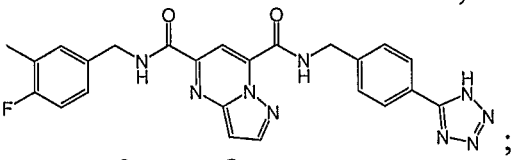
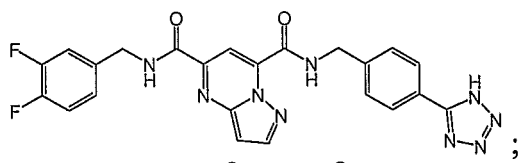
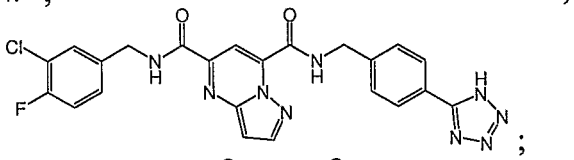
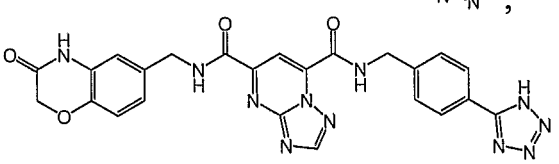
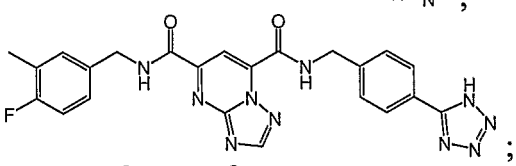
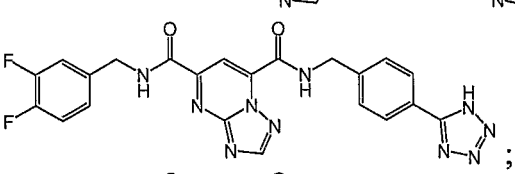
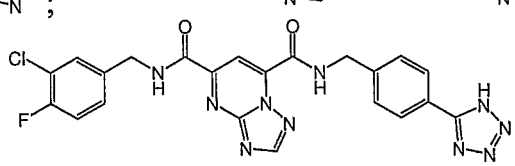
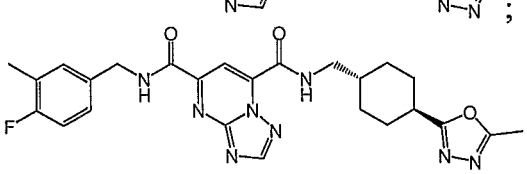
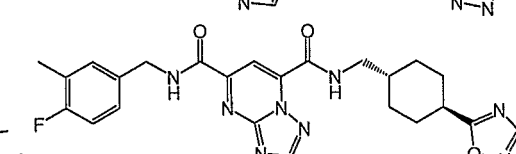
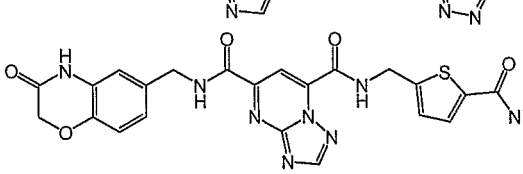
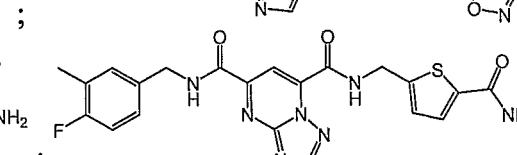
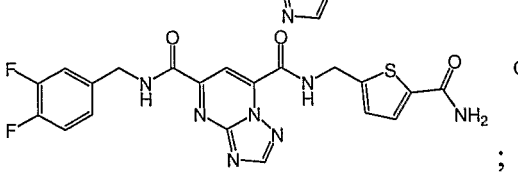
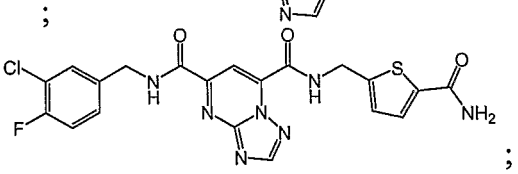
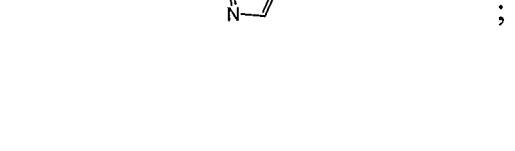
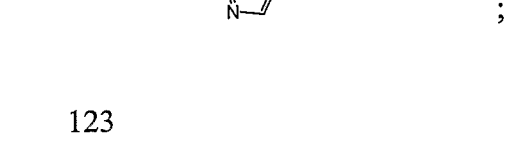


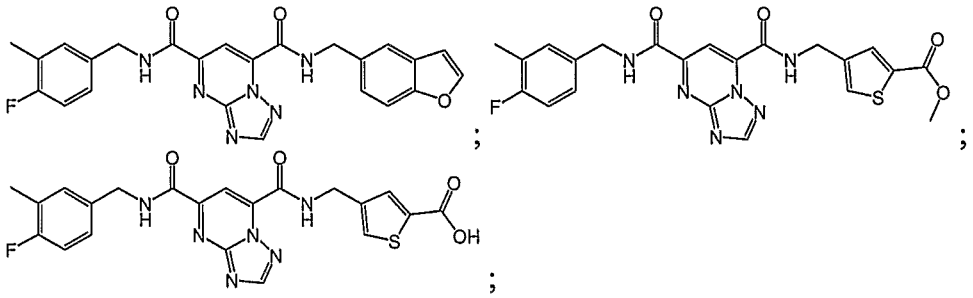

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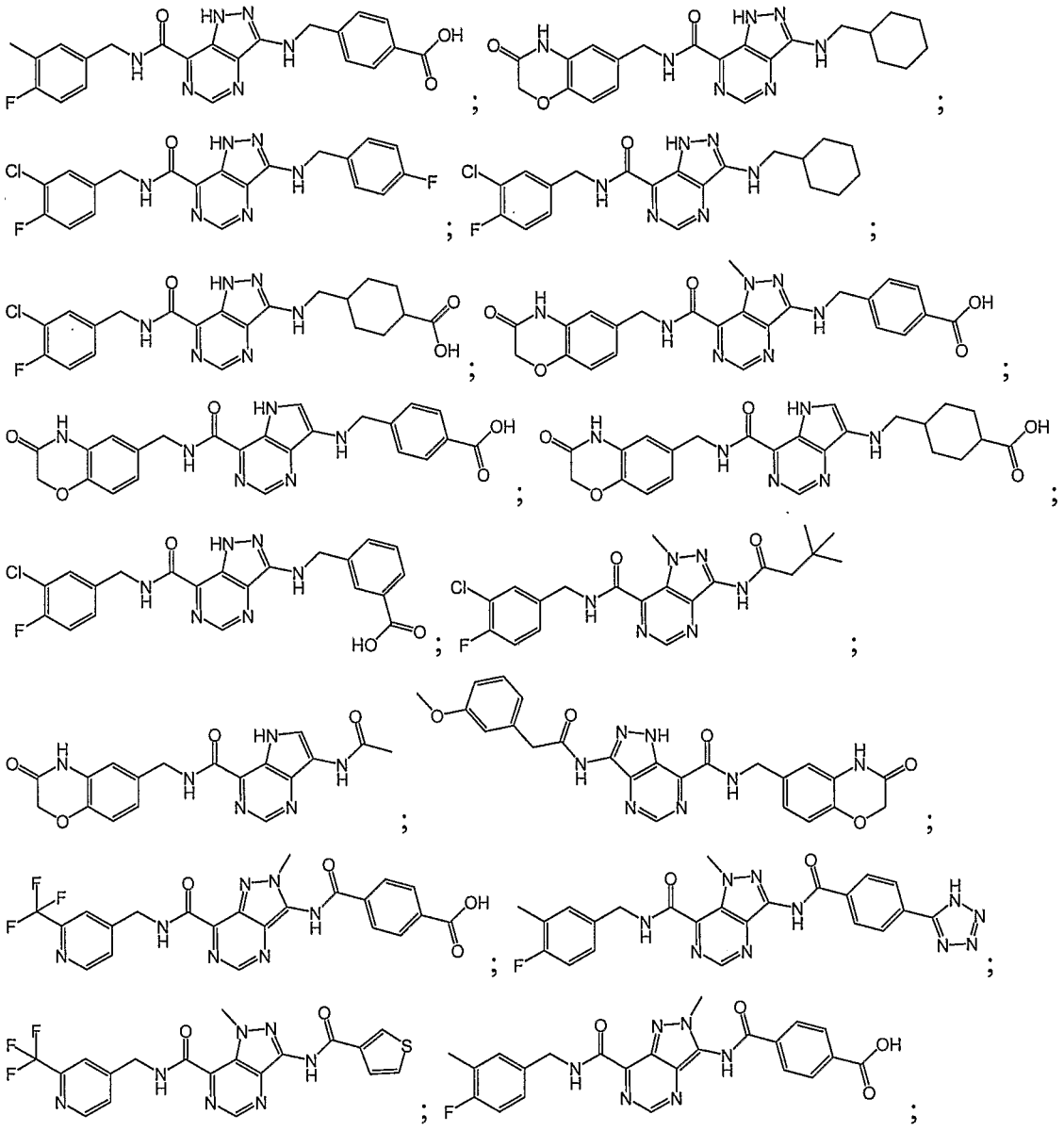
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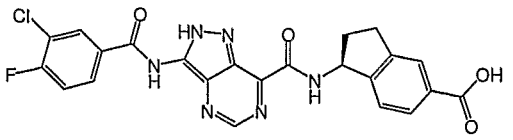
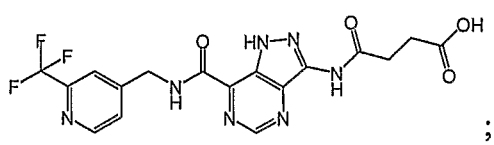
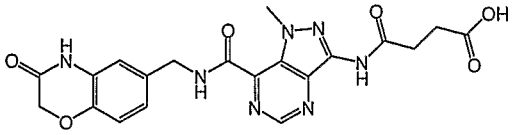
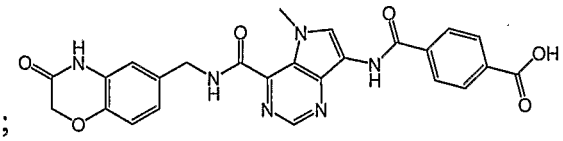
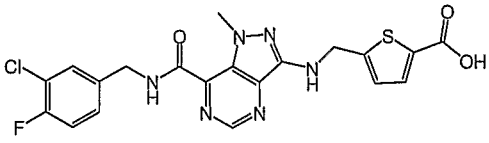
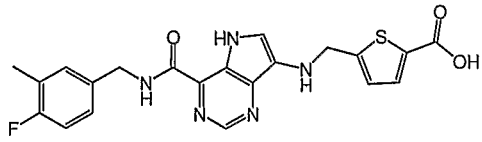
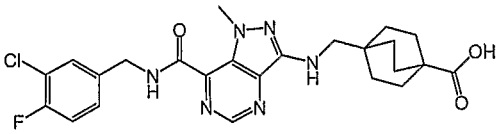
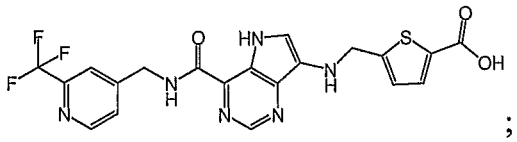
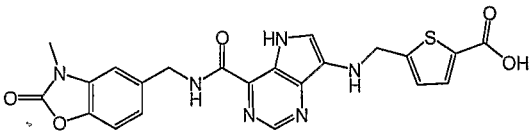
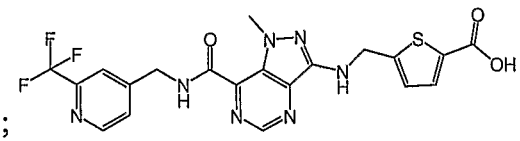
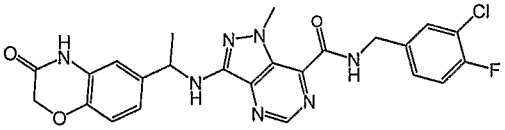
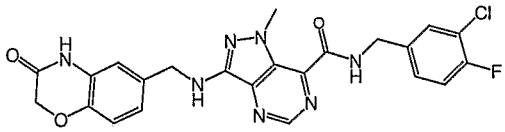
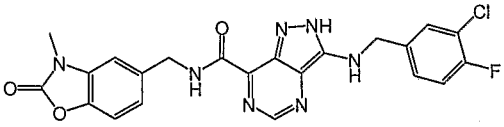
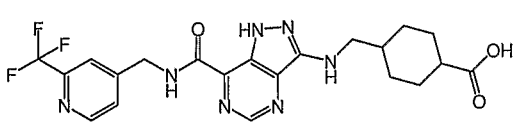
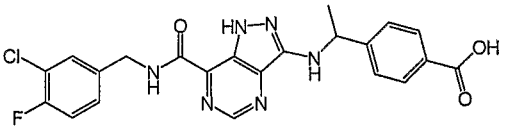
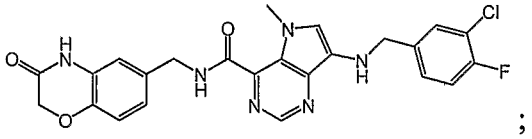
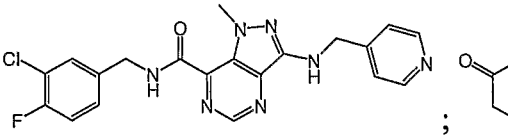
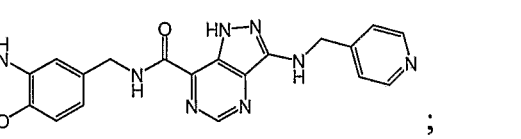
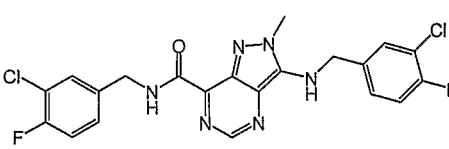
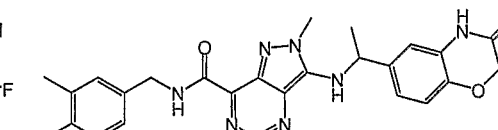
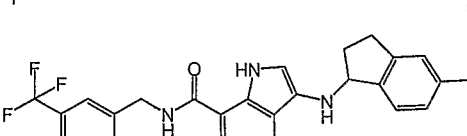
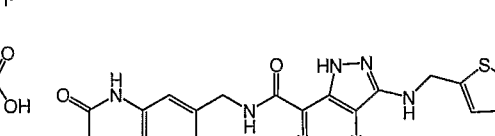
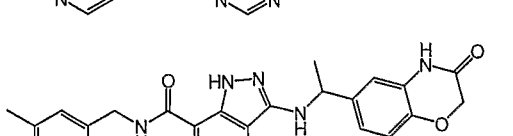
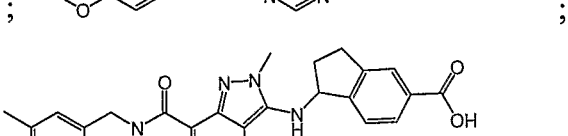
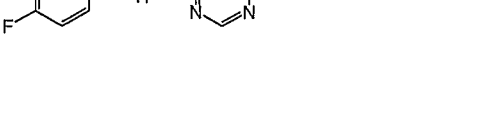
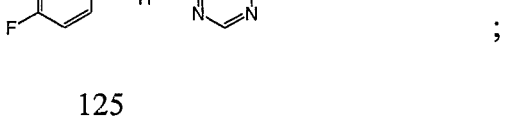

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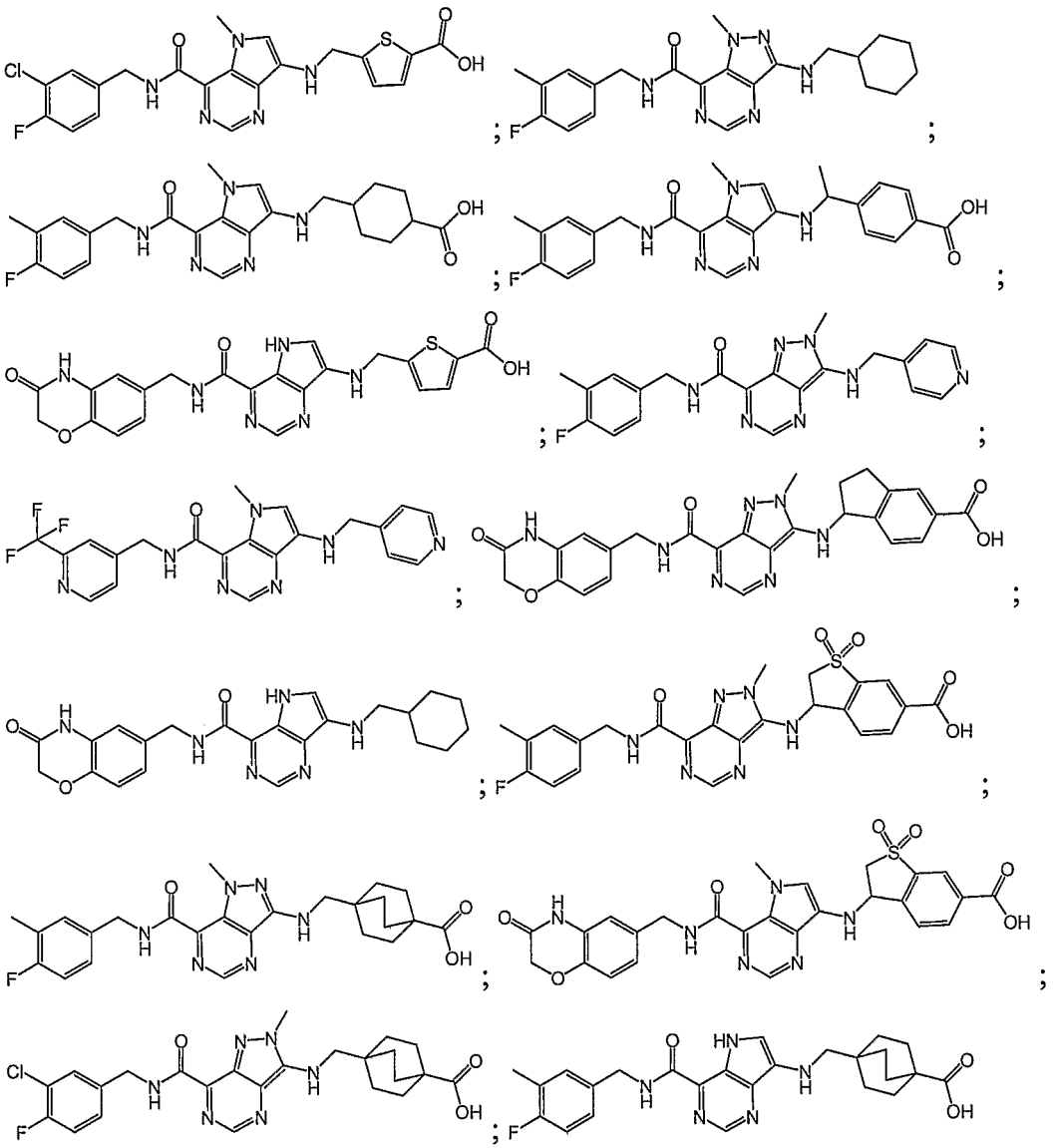


or a pharmaceutically acceptable salt thereof.

[0158] In still a further embodiment, the present invention provides a compound selected from:

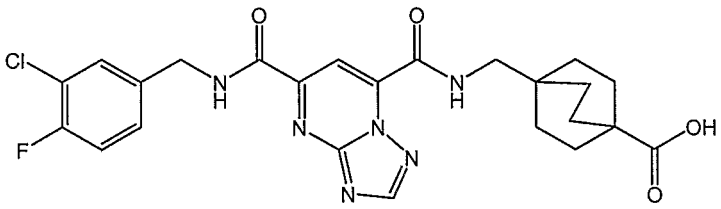



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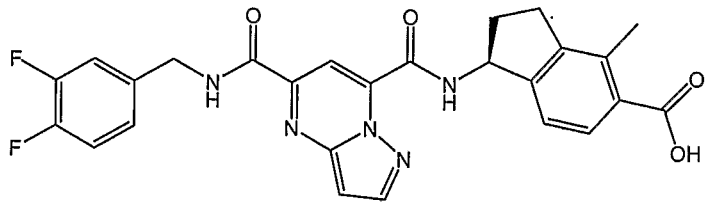
or a pharmaceutically acceptable salt thereof.

[0159] In one embodiment, the present invention provides a compound having the structure:



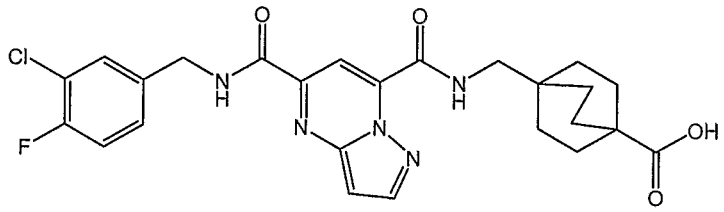
or a pharmaceutically acceptable salt thereof.

[0160] In another embodiment, the present invention provides a compound having the structure:



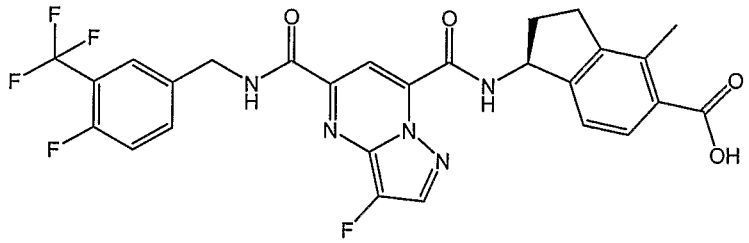
or a pharmaceutically acceptable salt thereof.

[0161] In yet another embodiment, the present invention provides a compound having the structure:



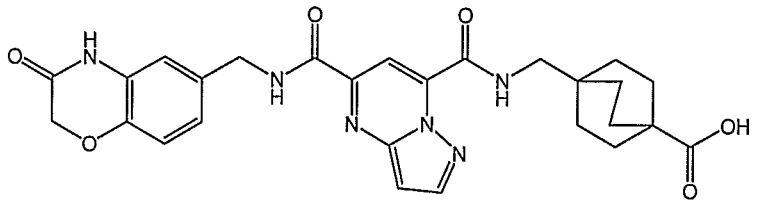
or a pharmaceutically acceptable salt thereof.

[0162] In still another embodiment, the present invention provides a compound having the structure:



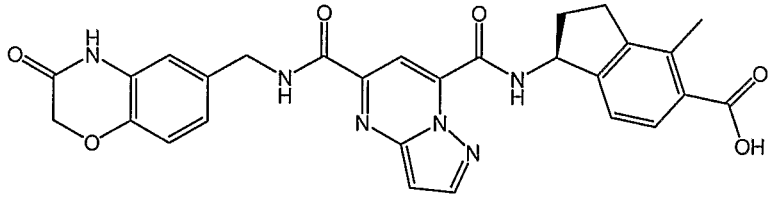
or a pharmaceutically acceptable salt thereof.

[0163] In a further embodiment, the present invention provides a compound having the structure:



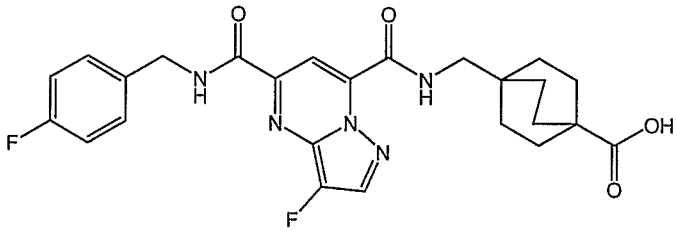
or a pharmaceutically acceptable salt thereof.

[0164] In yet a further embodiment, the present invention provides a compound having the structure:



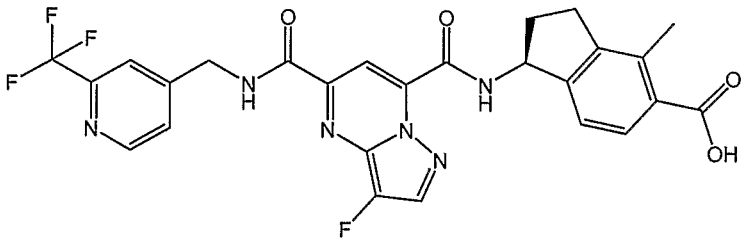
or a pharmaceutically acceptable salt thereof.

[0165] In still a further embodiment, the present invention provides a compound having the structure:



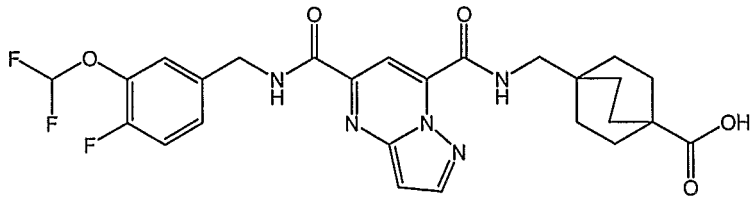
or a pharmaceutically acceptable salt thereof.

[0166] In another embodiment, the present invention provides a compound having the structure:



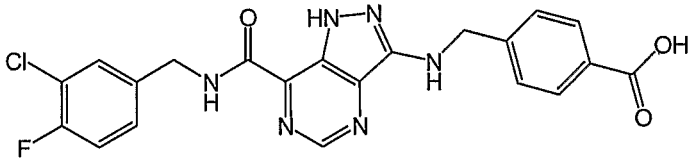
or a pharmaceutically acceptable salt thereof.

[0167] In yet another embodiment, the present invention provides a compound having the structure:



or a pharmaceutically acceptable salt thereof.

[0168] In still another embodiment, the present invention provides a compound having the structure:



or a pharmaceutically acceptable salt thereof.

[0169] The present invention is also directed to pharmaceutical compositions which include any of the amide containing heterobicyclic metalloproteases of the invention described hereinabove. In accordance therewith, some embodiments of the present invention provide a pharmaceutical composition which may include an effective amount of an amide containing heterobicyclic metalloprotease compound of the present invention and a pharmaceutically acceptable carrier.

[0170] In one embodiment, the present invention provides a pharmaceutical composition including an effective amount of the compound of Formula (I) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof, and a pharmaceutically acceptable carrier.

[0171] In yet another embodiment, the present invention provides a pharmaceutical composition including an effective amount of the compound of Formula (II) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof, and a pharmaceutically acceptable carrier.

[0172] In another embodiment, the present invention provides a pharmaceutical composition including an effective amount of the compound of Formula (III) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof, and a pharmaceutically acceptable carrier.

[0173] In still another embodiment, the present invention provides a pharmaceutical composition including an effective amount of the compound of Formula (IV) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof, and a pharmaceutically acceptable carrier.

[0174] In a further embodiment, the present invention provides a pharmaceutical composition including an effective amount of the compound of Formula (V) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof, and a pharmaceutically acceptable carrier.

[0175] In yet a further embodiment, the present invention provides a pharmaceutical composition including an effective amount of the compound of Formula (VI) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof, and a pharmaceutically acceptable carrier.

[0176] The present invention is also directed to methods of inhibiting metalloproteases and methods of treating diseases or symptoms mediated by an metalloprotease enzyme, particularly an MMP-13 enzyme. Such methods include administering a multicyclic bis-amid metalloprotease inhibiting compound of the present invention, or a pharmaceutically acceptable salt thereof. Examples of diseases or symptoms mediated by an MMP-13 mediated enzyme include, but are not limited to, rheumatoid arthritis, osteoarthritis, abdominal aortic aneurysm, cancer, inflammation, atherosclerosis, multiple sclerosis, chronic obstructive pulmonary disease, ocular diseases, neurological diseases, psychiatric diseases, thrombosis, bacterial infection, Parkinson's disease, fatigue, tremor, diabetic retinopathy, vascular diseases of the retina, aging, dementia, cardiomyopathy, renal tubular impairment, diabetes, psychosis, dyskinesia, pigmentary abnormalities, deafness, inflammatory and fibrotic syndromes, intestinal bowel syndrome, allergies, Alzheimer's disease, arterial plaque formation, viral infection, stroke, atherosclerosis, cardiovascular disease, reperfusion injury, trauma, chemical exposure or oxidative damage to tissues.

[0177] In one embodiment, the present invention provides a method of inhibiting MMP-13, which includes administering to a subject in need of such treatment a compound of Formula (I) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

[0178] In another embodiment, the present invention provides a method of inhibiting MMP-13, which includes administering to a subject in need of such treatment a compound of Formula (II) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

[0179] In yet another embodiment, the present invention provides a method of inhibiting MMP-13, which includes administering to a subject in need of such treatment a compound of Formula (III) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

[0180] In still another embodiment, the present invention provides a method of inhibiting MMP-13, which includes administering to a subject in need of such treatment a compound of Formula (IV) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

[0181] In a further embodiment, the present invention provides a method of inhibiting MMP-13, which includes administering to a subject in need of such treatment a compound of Formula (V) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

[0182] In yet a further embodiment, the present invention provides a method of inhibiting MMP-13, which includes administering to a subject in need of such treatment a compound of Formula (VI) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

[0183] In still a further embodiment, the present invention provides a method of treating an MMP-13 mediated disease, which includes administering to a subject in need of such treatment an effective amount of a compound of Formula (I) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

[0184] In one embodiment, the present invention provides a method of treating an MMP-13 mediated disease, which includes administering to a subject in need of such treatment an effective amount of a compound of Formula (II) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

[0185] In another embodiment, the present invention provides a method of treating an MMP-13 mediated disease, which includes administering to a subject in need of such treatment an effective amount of a compound of Formula (III) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

[0186] In another embodiment, the present invention provides a method of treating an MMP-13 mediated disease, which includes administering to a subject in need of such treatment an effective amount of a compound of Formula (IV) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

[0187] In another embodiment, the present invention provides a method of treating an MMP-13 mediated disease, which includes administering to a subject in need of such treatment an effective amount of a compound of Formula (V) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

[0188] In another embodiment, the present invention provides a method of treating an MMP-13 mediated disease, which includes administering to a subject in need of such treatment an effective amount of a compound of Formula (VI) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

[0189] Illustrative of the diseases which may be treated with such methods are: rheumatoid arthritis, osteoarthritis, abdominal aortic aneurysm, cancer, inflammation, atherosclerosis, multiple sclerosis, chronic obstructive pulmonary disease, ocular diseases, neurological diseases, psychiatric diseases, thrombosis, bacterial infection, Parkinson's disease, fatigue, tremor, diabetic retinopathy, vascular diseases of the retina, aging, dementia,

cardiomyopathy, renal tubular impairment, diabetes, psychosis, dyskinesia, pigmentary abnormalities, deafness, inflammatory and fibrotic syndromes, intestinal bowel syndrome, allergies, Alzheimer's disease, arterial plaque formation, oncology, periodontal, viral infection, stroke, atherosclerosis, cardiovascular disease, reperfusion injury, trauma, chemical exposure or oxidative damage to tissues, wound healing, hemorroids, skin beautifying, pain, inflammatory pain, bone pain and joint pain.

[0190] In some embodiments, of the present invention, the amide containing heterobicyclic metalloprotease compounds defined above are used in the manufacture of a medicament for the treatment of a disease or symptom mediated by an MMP enzyme, particularly an MMP-13 enzyme.

[0191] In some embodiments, the amide containing heterobicyclic metalloprotease compounds defined above may be used in combination with a drug, active, or therapeutic agent such as, but not limited to: (a) a disease modifying antirheumatic drug, such as, but not limited to, methotrexate, azathioptrineluflunomide, penicillamine, gold salts, mycophenolate, mofetil, and cyclophosphamide; (b) a nonsteroidal anti-inflammatory drug, such as, but not limited to, piroxicam, ketoprofen, naproxen, indomethacin, and ibuprofen; (c) a COX-2 selective inhibitor, such as, but not limited to, rofecoxib, celecoxib, and valdecoxib; (d) a COX-1 inhibitor, such as, but not limited to, piroxicam; (e) an immunosuppressive, such as, but not limited to, methotrexate, cyclosporin, leflunimide, tacrolimus, rapamycin, and sulfasalazine; (f) a steroid, such as, but not limited to, p-methasone, prednisone, cortisone, prednisolone, and dexamethasone; (g) a biological response modifier, such as, but not limited to, anti-TNF antibodies, TNF-α antagonists, IL-1 antagonists, anti- CD40, anti-CD28, IL-10, and anti-adhesion molecules; and (h) other anti-inflammatory agents or therapeutics useful for the treatment of chemokine mediated diseases, such as, but not limited to, p38 kinase inhibitors, PDE4 inhibitors, TACE inhibitors, chemokine receptor antagonists, thalidomide, leukotriene inhibitors, and other small molecule inhibitors of pro-inflammatory cytokine production.

[0192] In one embodiment, the present invention provides a pharmaceutical composition which includes:

A) an effective amount of a compound of Formula (I) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof;

B) a pharmaceutically acceptable carrier; and

C) a member selected from: (a) a disease modifying antirheumatic drug; (b) a nonsteroidal anti-inflammatory drug; (c) a COX-2 selective inhibitor; (d) a COX-1 inhibitor; (e) an immunosuppressive; (f) a steroid; (g) a biological response modifier; and (h) a small molecule inhibitor of pro-inflammatory cytokine production.

[0193] In another embodiment, the present invention provides a pharmaceutical composition which includes:

A) an effective amount of a compound of Formula (II) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof;

B) a pharmaceutically acceptable carrier; and

C) a member selected from: (a) a disease modifying antirheumatic drug; (b) a nonsteroidal anti-inflammatory drug; (c) a COX-2 selective inhibitor; (d) a COX-1 inhibitor; (e) an immunosuppressive; (f) a steroid; (g) a biological response modifier; and (h) a small molecule inhibitor of pro-inflammatory cytokine production.

[0194] In still another embodiment, the present invention provides a pharmaceutical composition which includes:

A) an effective amount of a compound of Formula (III) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof;

B) a pharmaceutically acceptable carrier; and

C) a member selected from: (a) a disease modifying antirheumatic drug; (b) a nonsteroidal anti-inflammatory drug; (c) a COX-2 selective inhibitor; (d) a COX-1 inhibitor;

(e) an immunosuppressive; (f) a steroid; (g) a biological response modifier; and (h) a small molecule inhibitor of pro-inflammatory cytokine production.

[0195] In a further embodiment, the present invention provides a pharmaceutical composition which includes:

A) an effective amount of a compound of Formula (IV) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof;

B) a pharmaceutically acceptable carrier; and

C) a member selected from: (a) a disease modifying antirheumatic drug; (b) a nonsteroidal anti-inflammatory drug; (c) a COX-2 selective inhibitor; (d) a COX-1 inhibitor; (e) an immunosuppressive; (f) a steroid; (g) a biological response modifier; and (h) a small molecule inhibitor of pro-inflammatory cytokine production.

[0196] In yet a further embodiment, the present invention provides a pharmaceutical composition which includes:

A) an effective amount of a compound of Formula (V) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof;

B) a pharmaceutically acceptable carrier; and

C) a member selected from: (a) a disease modifying antirheumatic drug; (b) a nonsteroidal anti-inflammatory drug; (c) a COX-2 selective inhibitor; (d) a COX-1 inhibitor; (e) an immunosuppressive; (f) a steroid; (g) a biological response modifier; and (h) a small molecule inhibitor of pro-inflammatory cytokine production.

[0197] In yet a further embodiment, the present invention provides a pharmaceutical composition which includes:

A) an effective amount of a compound of Formula (VI) and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof;

B) a pharmaceutically acceptable carrier; and

C) a member selected from: (a) a disease modifying antirheumatic drug; (b) a nonsteroidal anti-inflammatory drug; (c) a COX-2 selective inhibitor; (d) a COX-1 inhibitor; (e) an immunosuppressive; (f) a steroid; (g) a biological response modifier; and (h) a small molecule inhibitor of pro-inflammatory cytokine production.

Inhibiting Activity

[0198] The inhibiting activity towards different metalloproteases of the heterobicyclic metalloprotease inhibiting compounds of the present invention may be measured using any suitable assay known in the art. A standard *in vitro* assay for measuring the metalloprotease inhibiting activity is described in Examples 1700 to 1704. The heterobicyclic metalloprotease inhibiting compounds show activity towards MMP-3, MMP-8, MMP-12, MMP-13, ADAMTS-4 and/or ADAMTS-5.

[0199] The heterobicyclic metalloprotease inhibiting compounds of the invention have an MMP-13 inhibition activity (IC_{50} MMP-13) ranging from below 0.1 nM to about 20 μM, and typically, from about 0.2 nM to about 2 μM. Heterobicyclic metalloprotease inhibiting compounds of the invention desirably have an MMP inhibition activity ranging from about 0.2 nM to about 20 nM. Table 1 lists typical examples of heterobicyclic metalloprotease inhibiting compounds of the invention that have an MMP-13 activity lower than 5 nM (Group A) and from 5 nM to 20 μM (Group B).

TABLE 1

Summary of MMP-13 Activity for Compounds

Group	Ex. #
A	32, 37, 49, 63, 66, 73, 115, 159, 235, 317, 318, 319, 322, 328, 332, 337, 339, 340, 341, 343, 346, 348, 349, 351, 358, 359, 365, 379, 395, 397, 398, 399, 402, 403, 418, 419, 423, 425, 428, 430, 440, 442, 443, 449, 453, 459, 469, 476, 480
B	3, 4, 36, 71, 86, 93, 113, 126, 156, 158, 161, 231, 244, 246, 280, 308, 323, 347, 355, 363, 367, 400, 411, 420, 432, 461, 464, 466, 467, 479, 483

[0200] The synthesis of metalloprotease inhibiting compounds of the invention and their biological activity assay are described in the following examples which are not intended to be limiting in any way.

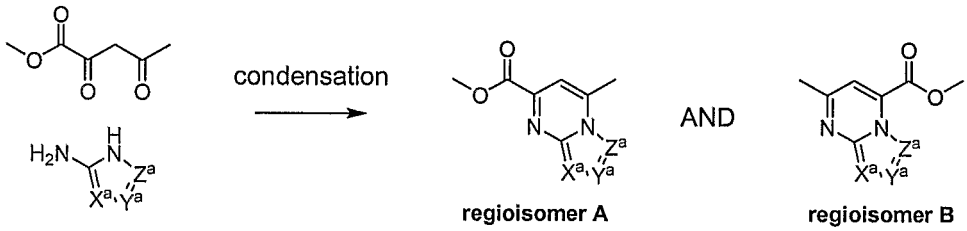
[0201] Schemes

[0202] Provided below are schemes according to which compounds of the present invention may be prepared. In schemes described herein, each of R^AR^B and R^CR^D may be the same or different, and each may independently be selected from R^1R^2 and $R^{20}R^{21}$ as defined

hereinabove. Each of X^a, Y^a, and Z^a shown in the schemes below may be the same or different, and each may independently be selected from N and CR^4. X^b shown in the schemes below in each occurrence may be the same or different and is independently selected from O, S, and NR^{51}. Y^b shown in the schemes below in each occurrence may be the same and is independently selected from CR^4 and N.

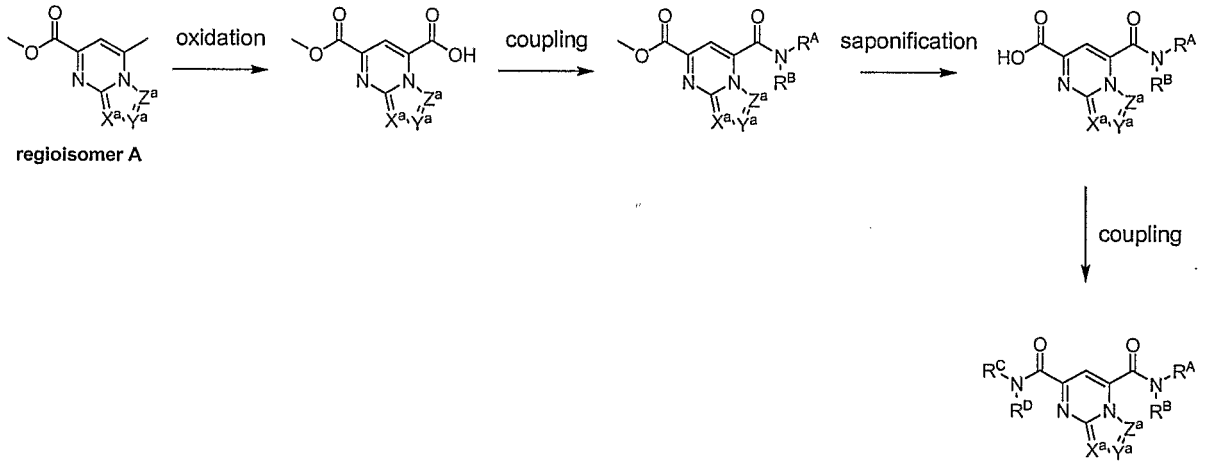
[0203] In some embodiments the compounds of Formula (I) –(III) are synthesized by the general methods shown in Scheme 1 to Scheme 3.

Scheme 1



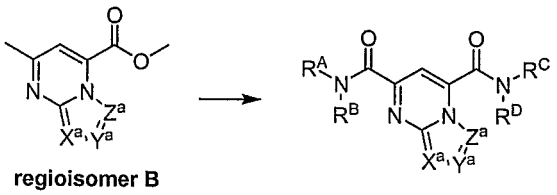
[0204] Methyl acetopyruvate is condensed (e.g. MeOH/reflux, aqueous HCl/100°C or glacial AcOH/95°C) with an amino substituted 5-membered heterocycle (e.g. 1*H*-pyrazol-5-amine) to afford a bicyclic ring system as a separable mixture of regioisomer A and regioisomer B (Scheme 1).

Scheme 2



[0205] The regioisomer A of the bicyclic ring system from Scheme 1 (e.g. 7-methyl-pyrazolo[1,5-*a*]pyrimidine-5-carboxylic acid methyl ester) is oxidized (e.g. selenium dioxide/120-130°C and then oxone®/room temperature) to afford the corresponding carboxylic acid (Scheme 2). Activated acid coupling (e.g. oxalyl chloride, PyBOP, PyBrOP, EDCI/HOAt or HATU/HOAt) with R^AR^BNH (e.g. 4-fluoro-3-methyl-benzylamine) in a suitable solvent gives the desired amide after purification. Saponification (e.g. aqueous LiOH/dioxane, NaOH/MeOH or TMSnOH/80°C) and further activated acid coupling (e.g. oxalyl chloride, PyBOP, PyBrOP, EDCI/HOAt, HATU/HOAt, *N*-cyclohexyl-carbodiimide-*N'*-methyl-polystyrene or polystyrene-IIDQ) with R^CR^DNH gives the desired bicyclic bisamide inhibitor after purification. If necessary, the R group can be further manipulated (e.g. saponification of a COOMe group in R).

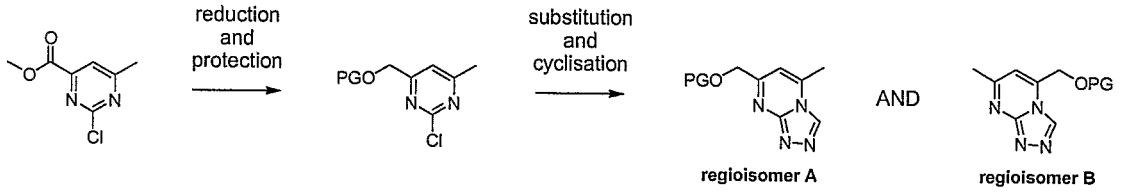
Scheme 3



[0206] The regioisomer B of the bicyclic ring system from Scheme 1 (e.g. 5-methyl-pyrazolo[1,5-*a*]pyrimidine-7-carboxylic acid methyl ester) is treated similarly as shown in Scheme 2 to give the desired bicyclic bisamide inhibitor after purification (Scheme 3). If necessary, the R group can be further manipulated (e.g. saponification of a COOMe group in R).

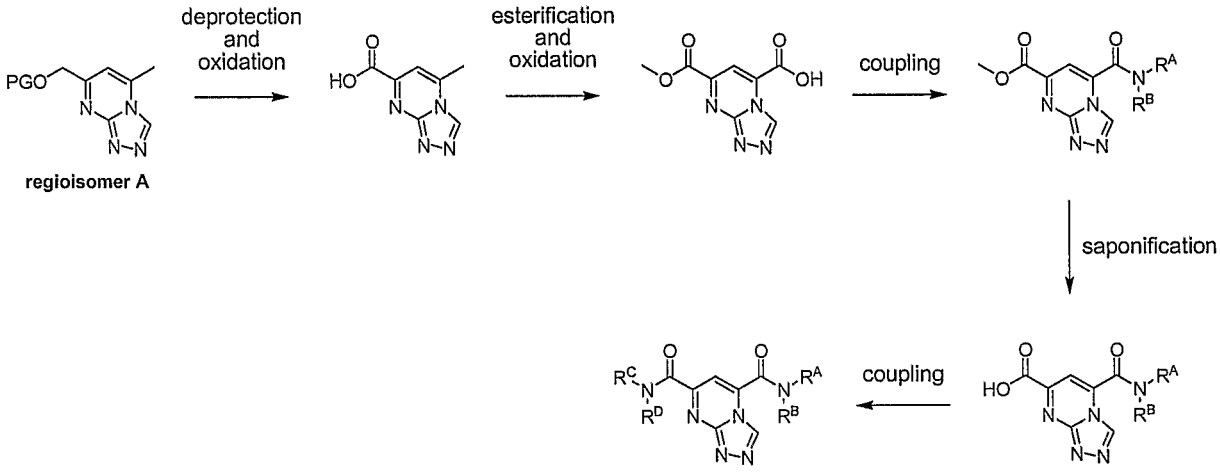
[0207] In some embodiments the compounds of Formula (I) – (III) are synthesized by the general methods shown in Scheme 4 to Scheme 8.

Scheme 4



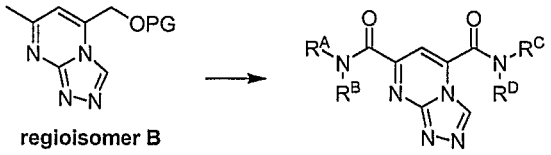
[0208] 2-Chloro-6-methyl-pyrimidine-4-carboxylic acid methyl ester is reduced (e.g. $NaBH_4$/MeOH) to the corresponding alcohol and protected with a suitable protecting group [PG, e.g. (2-methoxyethoxy)methyl] (Scheme 4). The obtained intermediate is stirred with hydrazine hydrate at 70°C to afford the corresponding hydrazino pyrimidine after concentration. Cyclization with a suitable reagent (e.g. triethylortho formate) gives the protected hydroxymethyl substituted bicyclic ring system as a separable mixture of regioisomer A and regioisomer B.

Scheme 5



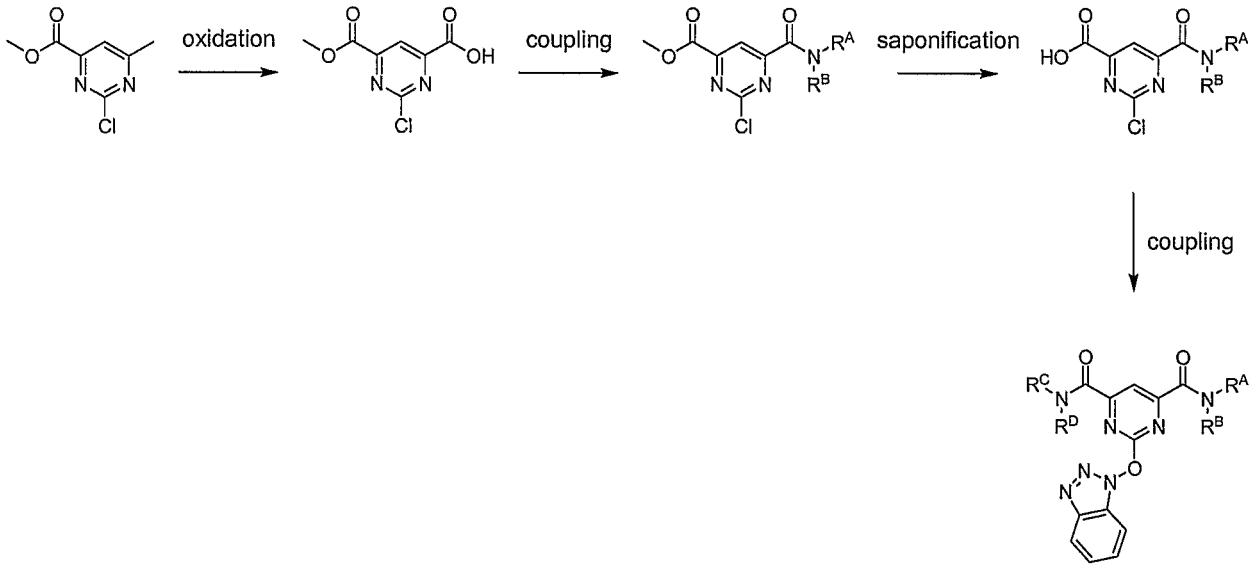
[0209] The regioisomer A of the protected hydroxymethyl substituted bicyclic ring system from Scheme 4 (e.g. 7-(2-methoxy-ethoxymethoxymethyl)-5-methyl-[1,2,4]triazolo[4,3-*a*]pyrimidine) is deprotected (e.g. HCl/THF) and then oxidized (e.g. $KMnO_4$ in aqueous Na_2CO_3/50°C) to afford the corresponding carboxy substituted bicyclic ring system (Scheme 5). Esterifcation (e.g. thionyl chloride/MeOH) and oxidation (e.g. selenium dioxide/70°C) of this intermediate gives the corresponding carboxylic acid. Activated acid coupling (e.g. oxalyl chloride, PyBOP, PyBrOP, EDCI/HOAt or HATU/HOAt) with R^AR^BNH (e.g. 4-fluoro-3-methyl-benzylamine) in a suitable solvent gives the desired amide after purification. Saponification (e.g. aqueous LiOH/dioxane, NaOH/MeOH or TMSnOH/80°C) and further activated acid coupling (e.g. oxalyl chloride, PyBOP, PyBrOP, EDCI/HOAt, HATU/HOAt) with R^CR^DNH gives the desired bicyclic bisamide inhibitor after purification. If necessary, the R group can be further manipulated (e.g. saponification of a COOMe group in R).

Scheme 6



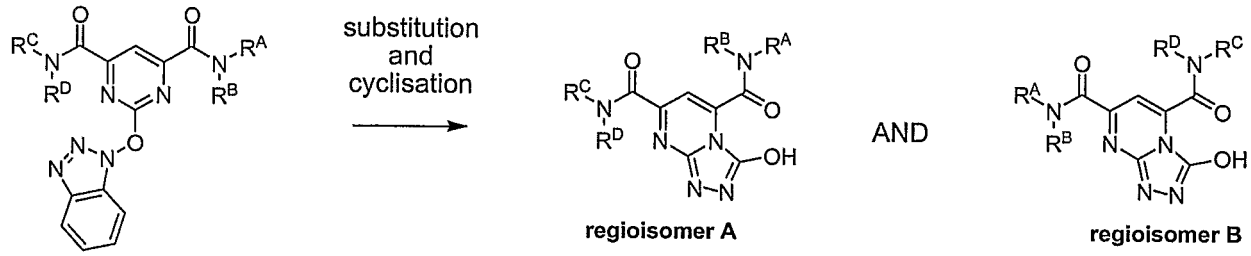
[0210] The regioisomer B of the protected hydroxymethyl substituted bicyclic ring system from Scheme 4 (e.g. 5-(2-methoxy-ethoxymethoxymethyl)-7-methyl-[1,2,4]triazolo[4,3-*a*]pyrimidine) is treated similarly as shown in Scheme 5 to give the desired bicyclic bisamide inhibitor after purification (Scheme 6). If necessary, the R group can be further manipulated (e.g. saponification of a.COOMe group in R).

Scheme 7



[0211] 2-Chloro-6-methyl-pyrimidine-4-carboxylic acid methyl ester is oxidized (e.g. selenium dioxide/105°C) to the corresponding carboxylic acid (Scheme 7). Activated acid coupling (e.g. oxalyl chloride) with R^AR^BNH (e.g. 4-fluoro-3-methyl-benzylamine) in a suitable solvent gives the desired amide after purification. Saponification (e.g. aqueous LiOH/THF) and further activated acid coupling (e.g. PyBOP) with R^CR^DNH (e.g. 4-aminomethyl-benzoic acid methyl ester) gives the corresponding benzotriazol-1-yloxy substituted pyrimidine bisamide.

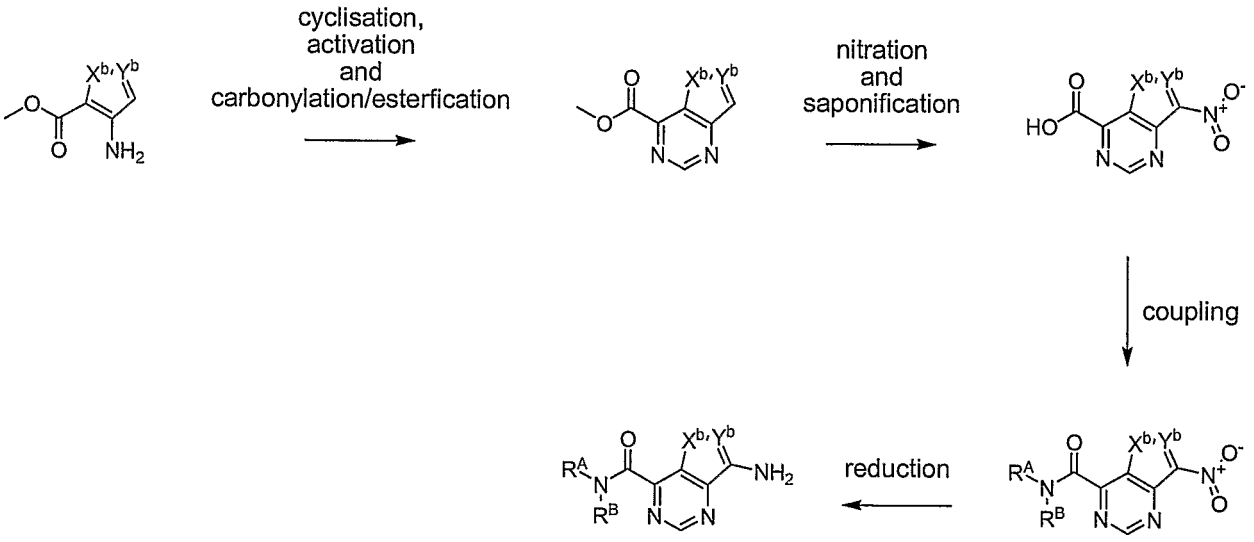
Scheme 8



[0212] A benzotriazol-1-yloxy substituted pyrimidine bisamide from Scheme 7 (e.g. 4-({[2-(benzotriazol-1-yloxy)-6-(4-fluoro-3-methyl-benzylcarbamoyl)-pyrimidine-4-carbonyl]-amino}-methyl)-benzoic acid methyl ester) is stirred with hydrazine hydrate at room temperature to afford the corresponding hydrazino pyrimidine bisamide after concentration (Scheme 8). Cyclization with a suitable reagent (e.g. phosgene) gives the corresponding bicyclic bisamide inhibitor as a mixture of regioisomer A and regioisomer B. If necessary, the R group can be further manipulated (e.g. saponification of a COOMe group in R).

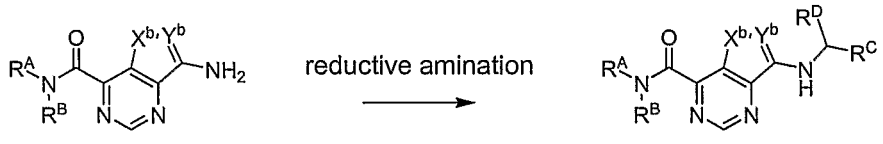
[0213] In some embodiments the compounds of Formula (IV) – (VI) are synthesized by the general methods shown in Scheme 9 to Scheme 11.

Scheme 9



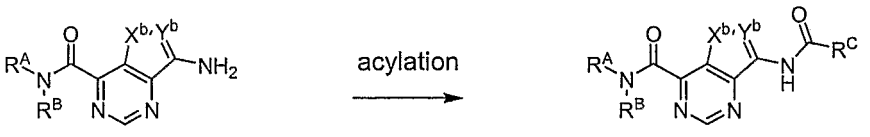
[0214] An ester and amino substituted heterocycle (e.g. 3-amino-1*H*-pyrrole-2-carboxylic acid ethyl ester) is condensed (e.g. EtOH/reflux) with formamidine to give a hydroxy substituted bicyclic ring system (Scheme 9). This intermediate is then converted into the corresponding bromo derivative using a suitable reagent (e.g. $POBr_3$/80°C). The resulting bromide is heated to (e.g. 80°C) with a suitable catalyst (e.g. $Pd(OAc)_2$, dppf) and base (e.g. Et_3N) under a carbon monoxide atmosphere in a suitable solvent (e.g. MeOH) to give the corresponding bicyclic methylester after purification. Nitration (e.g. concentrated HNO_3/0°C to room temperature) and saponification (e.g. aqueous LiOH) gives the corresponding nitro substituted bicyclic carboxylic acid. Activated acid coupling (e.g. EDCI/HOAt) with R^AR^BNH (e.g. 6-aminomethyl-4*H*-benzo[1,4]oxazin-3-one) in a suitable solvent gives the desired amide. This intermediate is stirred with a suitable catalyst (e.g. Pd/C) and acid (e.g. AcOH) under a hydrogen atmosphere to afford corresponding amino substituted bicyclic amide after purification.

Scheme 10



[0215] The amino substituted bicyclic amide from scheme 9 (e.g. 3-amino-1*H*-pyrazolo[4,3-*d*]pyrimidine-7-carboxylic acid 3-chloro-4-fluoro-benzylamide) and the carbonyl compound $(CO)R^CR^D$ (e.g. 4-fluorobenzaldehyde) is stirred with a suitable reducing agent (e.g. $NaCNBH_3$) and a small amount of acid (e.g. AcOH) in a suitable solvent (e.g. MeOH) to give the corresponding bicyclic inhibitor after purification (Scheme 10). If necessary, the R group can be further manipulated (e.g. saponification of a COOMe group in R).

Scheme 11



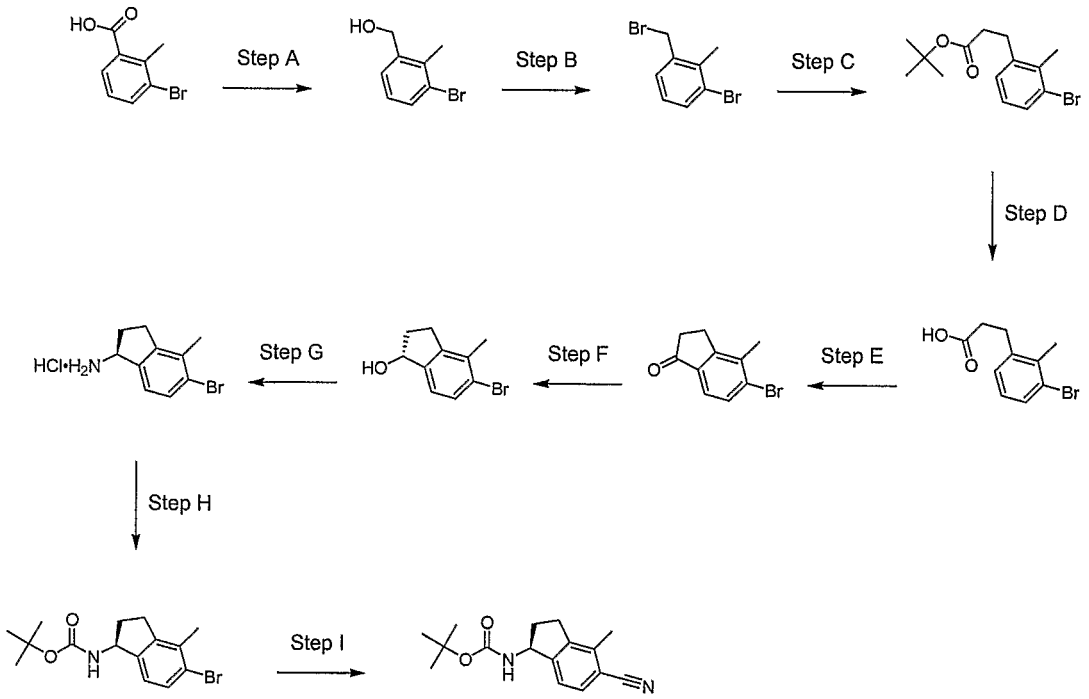
[0216] The amino substituted bicyclic amide from scheme 9 (e.g. 7-amino-5*H*-pyrrolo[3,2-*d*]pyrimidine-4-carboxylic acid (3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-6-ylmethyl)-amide is stirred with the acid chloride R^CCOCl or with the acid anhydride $(R^CCO)_2O$ (e.g. acetic anhydride) in a suitable solvent (e.g. pyridine) to give the corresponding bicyclic inhibitor after purification (Scheme 11). If necessary, the R group can be further manipulated (e.g. saponification of a COOMe group in R).

EXAMPLES AND METHODS

[0217] All reagents and solvents were obtained from commercial sources and used without further purification. Proton spectra (^{1}H-NMR) were recorded on a 400 MHz and a 250 MHz NMR spectrometer in deuterated solvents. Purification by column chromatography was performed using silica gel, grade 60, 0.06-0.2 mm (chromatography) or silica gel, grade 60, 0.04-0.063 mm (flash chromatography) and suitable organic solvents as indicated in specific examples. Preparative thin layer chromatography was carried out on silica gel plates with UV detection.

[0218] Preparative Examples 1-835 are directed to intermediate compounds useful in preparing the compounds of the present invention.

Preparative Example 1



[0219] Step A

Under a nitrogen atmosphere a 1M solution of BH_3•THF complex in THF (140 mL) was added dropwise over a 3 h period to an ice cooled solution of commercially available 3-bromo-2-methyl-benzoic acid (20.0 g) in anhydrous THF (200 mL). Once gas evolution had subsided, the cooling bath was removed and mixture stirred at room temperature for 12 h. The mixture was then poured into a mixture of 1N aqueous HCl (500 mL) and ice and then extracted with Et_2O (3 x 150 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated to afford the title compound as a colorless solid (18.1 g, 97%). ^{1}H-NMR ($CDCl_3$) □= 7.50 (d, 1 H), 7.30 (d, 1 H), 7.10 (t, 1 H), 4.70 (s, 2 H), 2.40 (s, 3 H).

[0220] Step B

Under a nitrogen atmosphere PBr_3 (5.52 mL) was added over a 10 min period to an ice cooled solution of the title compound from Step A above (18.1 g) in anhydrous CH_2Cl_2 (150 mL). The cooling bath was removed and mixture stirred at room temperature for 12 h. The mixture was cooled (0-5°C), quenched by dropwise addition of MeOH (20 mL), washed with saturated aqueous $NaHCO_3$ (2 x 150 mL), dried ($MgSO_4$), filtered and concentrated to afford the title compound as a viscous oil (23.8 g, 97%). ^{1}H-NMR ($CDCl_3$) □= 7.50 (d, 1 H), 7.25 (d, 1 H), 7.00 (t, 1 H), 4.50 (s, 2 H), 2.50 (s, 3 H).

[0221] Step C

Under a nitrogen atmosphere a 1.5M solution of lithium diispropylamide in cyclohexane (63 mL) was added dropwise to a cooled (–78°C, acetone/dry ice) solution of ^{t}BuOAc in anhydrous THF (200 mL). The mixture was stirred at –78°C for 1 h, then a solution of the title compound from Step B above (23.8 g) in THF (30 mL) was added and the mixture was stirred for 12 h while warming to room temperature. The mixture was concentrated, diluted with Et_2O (300 mL), washed with 0.5N aqueous HCl (2 x 100 mL), dried ($MgSO_4$), filtered and concentrated to afford the title compound as a pale-yellow viscous oil (21.5 g, 80%). ^{1}H-NMR ($CDCl_3$) □= 7.50 (d, 1 H), 7.25 (d, 1 H), 7.00 (t, 1 H), 3.00 (t, 2 H), 2.50 (t, 2 H), 2.40 (s, 3 H), 1.50 (s, 9 H).

[0222] Step D

A mixture of the title compound from Step C above (21.5 g) and polyphosphoric acid (250 g) was placed in a preheated oil bath (140°C) for 10 min while mixing the thick slurry occasionally with a spatula. The oil bath was removed, ice and H_2O (1 L) was added and the mixture was stirred for 2 h. The precipitate was isolated by filtration, washed with H_2O (2 x 100 mL) and dried to afford the title compound (16.7 g, 96%). ^{1}H-NMR ($CDCl_3$) □= 7.50 (d, 1 H), 7.20 (d, 1 H), 7.00 (t, 1 H), 3.00 (t, 2 H), 2.65 (t, 2 H), 2.40 (s, 3 H).

[0223] Step E

Under a nitrogen atmosphere oxalyl chloride (12.0 mL) was added dropwise to an ice cooled solution of the title compound from Step D above (11.6 g) in anhydrous CH_2Cl_2 (100 mL). The resulting mixture was stirred for 3 h and then concentrated. The remaining dark residue was dissolved in anhydrous CH_2Cl_2 (300 mL) and $AlCl_3$ (6.40 g) was added. The mixture was heated to reflux for 4 h, cooled and poured into ice water (500 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated to afford the title compound as a light brown solid (10.6 g, 98%). ^{1}H-NMR ($CDCl_3$) □= 7.65 (d, 1 H), 7.50 (d, 1 H), 3.05 (t, 2 H), 2.70 (t, 2 H), 2.40 (s, 3 H).

[0224] Step F

Using a syringe pump, a solution of the title compound from Step E above (9.66 g) in anhydrous CH_2Cl_2 (70 mL) was added over a 10 h period to a cooled (–20°C, internal temperature) mixture of a 1M solution of (*S*)-(–)-2-methyl-CBS-oxazaborolidine in toluene (8.6 mL) and a 1M solution of BH_3•Me_2S complex in CH_2Cl_2 (43.0 mL) in CH_2Cl_2 (200 mL). The mixture was then quenched at –20°C by addition of MeOH (100 mL), warmed to room temperature, concentrated and purified by flash chromatography (silica, Et_2O/CH_2Cl_2) to afford the title compound as a colorless solid (8.7 g, 90%). ^{1}H-NMR ($CDCl_3$) □= 7.50 (d, 1 H), 7.20 (d, 1 H), 5.25 (m, 1 H), 3.10 (m, 1 H), 2.90 (m, 1 H), 2.50 (m, 1 H), 2.35 (s, 3 H), 2.00 (m, 1 H).

[0225] Step G

Under a nitrogen atmosphere NEt_3 (15.9 mL) and methanesulfonyl chloride (4.5 mL) were added subsequently to a cooled (–78°C, acetone/dry ice) solution of the title compound

from Step F above (8.7 g) in anhydrous CH_2Cl_2 (200 mL). The mixture was stirred at –78°C for 90 min, then NH_3 (~150 mL) was condensed into the mixture using a dry ice condenser at a rate of ~3 mL/min and stirring at –78°C was continued for 2 h. Then the mixture was gradually warmed to room temperature allowing the NH_3 to evaporate. 1N aqueous NaOH (200 mL) was added, the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated. The remaining light brown oil was dissolved in Et_2O (200 mL) and a 4M solution of HCl in 1,4-dioxane (10 mL) was added. The formed precipitate was collected and dried to give the title compound (9.0 g, 90%). $[M\text{-}NH_3Cl]^+ = 209/211$.

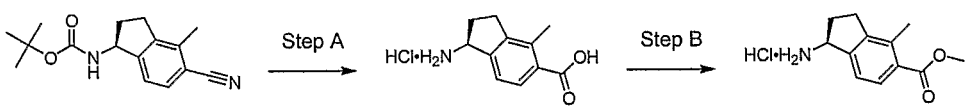
[0226] Step H

To an ice cooled solution of the title compound from Step G above (5.2 g) in anhydrous CH_2Cl_2 (50 mL) were subsequently added di-*tert*-butyl dicarbonate (5.0 g) and NEt_3 (9.67 mL). The resulting mixture was stirred for 3 h, concentrated, diluted with Et_2O (250 mL), washed with saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous NaCl (100 mL), dried ($MgSO_4$), filtered and concentrated to afford the title compound as a colorless solid (7.28 g, 97%). ^{1}H-NMR ($CDCl_3$, free base) □= 7.40 (m, H), 7.00 (d, 1 H), 4.30 (t, 1 H) 2.90 (m, 1 H), 2.80 (m, 1 H), 2.60 (m, 1 H), 2.30 (s, 3 H), 1.80 (m, 1 H).

[0227] Step I

Under a nitrogen atmosphere a mixture of the title compound from Step H above (7.2 g), $Zn(CN)_2$ (5.2 g) and $Pd(PPh_3)_4$ (2.6 g) in anhydrous DMF (80 mL) was heated to 100°C for 18 h, concentrated and purified by flash chromatography (silica, CH_2Cl_2/EtOAc) to afford the title compound as an off-white solid (4.5 g, 75%). ^{1}H-NMR ($CDCl_3$) □= 7.50 (d, 1 H), 7.20 (d, 1 H), 5.15 (m, 1 H), 4.75 (m, 1 H), 2.95 (m, 1 H), 2.80 (m, 1 H), 2.70 (m, 1 H), 2.40 (s, 3 H), 1.90 (m, 1 H), 1.50 (s, 9 H).

Preparative Example 2



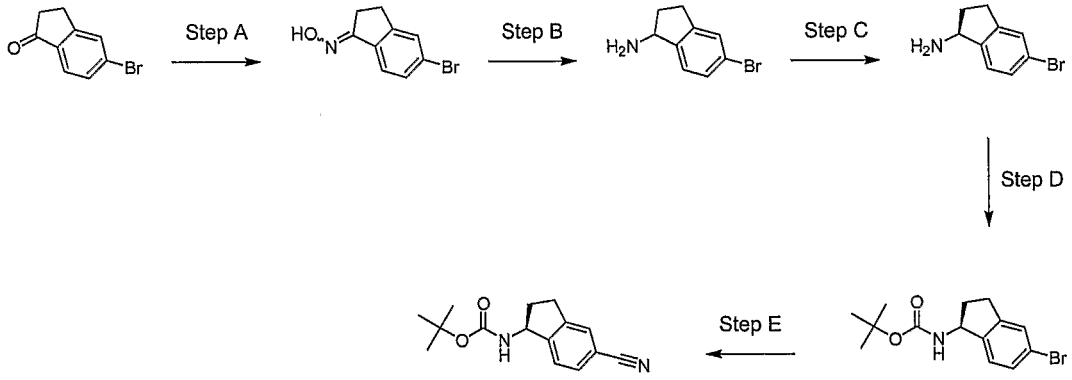
[0228] Step A

The title compound from the Preparative Example 1, Step I (1.0 g) was suspended in 6N aqueous HCl (20 mL), heated to 100°C for 12 h and concentrated to give the title compound as a colorless solid. (834 mg, >99%). $[M\text{-}NH_3Cl]^+ = 175$.

[0229] Step B

Anhydrous HCl gas was bubbled through an ice cooled solution of the title compound from Step A above (1.0 g) in anhydrous MeOH (20 mL) for 2-3 min. The cooling bath was removed, the mixture was heated to reflux for 12 h, cooled to room temperature and concentrated to give the title compound as a colorless solid (880 mg, 83%). $[M\text{-}NH_3Cl]^+ = 189$.

Preparative Example 3



[0230] Step A

A mixture of commercially available 5-bromo-indan-1-one (1.76 g), hydroxylamine hydrochloride (636 mg) and NaOAc (751 mg) in MeOH (40 mL) was stirred at room temperature for 16 h and then diluted with H_2O (100 mL). The formed precipitate was collected by filtration, washed with H_2O (3 x 20 mL) and dried to afford the title compound as a colorless solid (1.88 g, >99%). $[MH]^+ = 226/228$.

[0231] Step B

Under an argon atmosphere a 1M solution of $LiAlH_4$ in Et_2O (42.4 mL) was slowly added to a cooled (–78°C, acetone/dry ice) solution of the title compound from Step A above (1.88 g) in Et_2O (20 mL). Then the cooling bath was removed and the mixture was heated to

reflux for 5 h. The mixture was cooled (0-5°C) and H_2O (1.6 mL), 15% aqueous NaOH (1.6 mL) and H_2O (4.8 mL) were carefully and sequentially added. The resulting mixture was filtered through a plug of celite® and concentrated to give the title compound as a clear oil (1.65 g, 94%). $[MH]^+ = 212/214$.

[0232] Step C

To a boiling solution of the title compound from Step B above (1.13 g) in MeOH (2.3 mL) was added a hot solution of commercially available *N*-acetyl-L-leucine (924 mg) in MeOH (3 mL). The solution was allowed to cool to room temperature, which afforded a white precipitate. The precipitate was collected by filtration, washed with MeOH (2 mL) and recrystalized from MeOH (2 x). The obtained solid was dissolved in a mixture of 10% aqueous NaOH (20 mL) and Et_2O (20 mL), the organic phase was separated and the aqueous phase was extracted with Et_2O. The combined organic phases were dried ($MgSO_4$), filtered and concentrated to give the title compound as a clear oil (99 mg, 18%). $[MH]^+ = 212/214$.

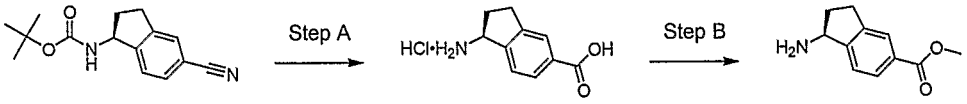
[0233] Step D

To a solution of the title compound from Step C above (300 mg) in THF (10 mL) were subsequently added di-*tert*-butyl dicarbonate (370 mg) and NEt_3 (237 μL). The resulting mixture was stirred at room temperature for 16 h, concentrated and purified by chromatography (silica, hexanes/EtOAc) to afford the title compound as a clear oil (460 mg, >99%). $[MNa]^+ = 334/336$.

[0234] Step E

Under an argon atmosphere a mixture of the title compound from Step D above (460 mg), $Zn(CN)_2$ (200 mg) and $Pd(PPh_3)_4$ (89 mg) in anhydrous DMF (5 mL) was heated in a sealed vial to 110°C for 18 h. The mixture was cooled to room temperature and diluted with Et_2O (20 mL) and H_2O (20 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (4 x 10 mL). The combined organic phases were washed with H_2O (3 x 10 mL) and saturated aqueous NaCl (10 mL), dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, hexanes/EtOAc) to afford the title compound as a clear oil (170 mg, 47%). $[MH]^+ = 259$.

Preparative Example 4



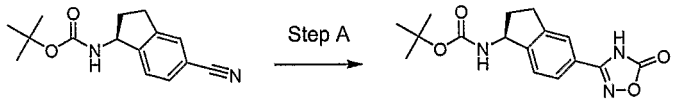
[0235] Step A

The title compound from the Preparative Example 3, Step E (1.0 g) was suspended in 6N aqueous HCl (50 mL), heated under closed atmosphere to 110-112°C for 20 h and concentrated to give the title compound (827 mg, >99%). $[M\text{-}Cl]^+ = 178$.

[0236] Step B

The title compound from Step A above (827 mg) was dissolved in anhydrous MeOH (150 mL) and saturated with anhydrous HCl gas. The resulting mixture was heated to reflux for 20 h, cooled to room temperature and concentrated. The remaining oil was taken up in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated to give the title compound as an oil which slowly crystallized into a light brown solid (660 mg, 89%). $[MH]^+ = 192$.

Preparative Example 5

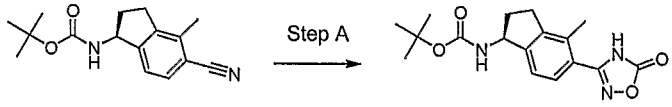


[0237] Step A

To a solution of hydroxylamine hydrochloride (2.78 g) in dry MeOH (100 mL) was added a 30wt% solution of NaOMe in MeOH (7.27 mL). The resulting white suspension was stirred at room temperature for 15 min and a solution of the title compound from the Preparative Example 3, Step E (5.17 g) in dry MeOH (100 mL) was added. The mixture was heated to reflux for 20 h (complete conversion checked by HPLC/MS, $[MH]^+ = 292$) and then cooled to room temperature. Diethyl carbonate (48.2 g) and a 30wt% solution of NaOMe in MeOH (7.27 mL) were added successively and the resulting mixture was heated to reflux for 24 h. The mixture was concentrated, diluted with 1M aqueous NH_4Cl (200 mL) and extracted with CH_2Cl_2/MeOH (60:40, 500 mL) and CH_2Cl_2 (3 x 200 mL). The combined organic layers

were dried ($MgSO_4$), filtered, concentrated and purified by flash chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a white solid (3.89 g, 61%) $[MNa]^+ = 340$.

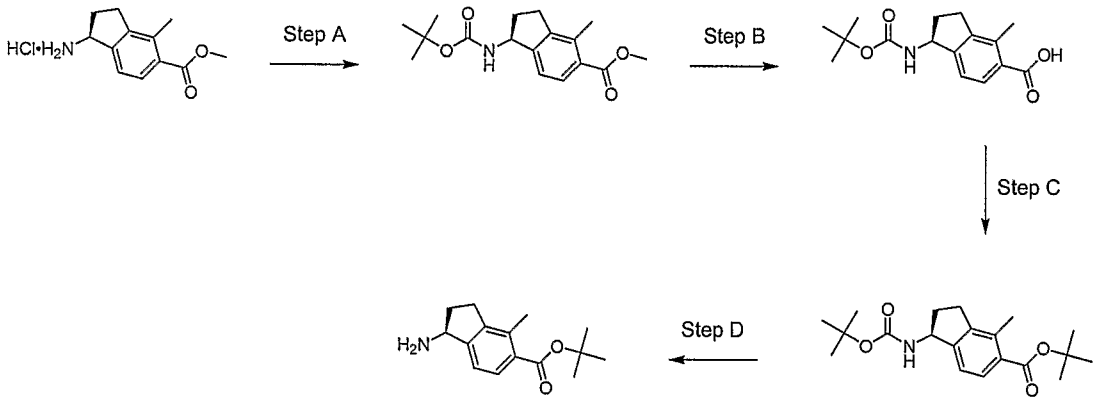
Preparative Example 6



[0238] Step A

The title compound from the Preparative Example 1, Step I (1.37 mg) was treated similarly as described in the Preparative Example 5, Step A to afford the title compound as a white solid (845 mg, 51%). $[MNa]^+ = 354$.

Preparative Example 7



[0239] Step A

To an ice cooled solution of the title compound from the Preparative Example 2, Step B (5.94 g) in dry CH_2Cl_2 (50 mL) were subsequently added di-*tert*-butyl dicarbonate (1.6 g) and NEt_3 (1 mL). The mixture was stirred for 3 h, concentrated, diluted with Et_2O (250 mL), washed with saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous NaCl (100 mL), dried ($MgSO_4$), filtered and concentrated to afford the title compound as a colorless solid (7.28 g, 97 %). $[MNa]^+ = 328$.

[0240] Step B

To a mixture of the title compound from Step A above (7.28 g) in THF (60 mL) was added 1M aqueous LiOH (60 mL). The mixture was stirred at 50°C for 2 h, concentrated, diluted with H_2O, adjusted to pH 5 with HCl and extracted with EtOAc. The combined organic phases were dried ($MgSO_4$), filtered and concentrated to afford the title compound as colorless solid (1.87 g, 27%). $[MNa]^+ = 314$.

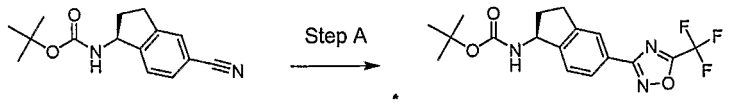
[0241] Step C

At 80°C *N,N*-dimethylformamide di-*tert*-butyl acetal (6.2 mL) was added to a solution of the title compound from Step B above (1.87 g) in dry toluene (15 mL). The mixture was stirred at 80°C for 3 h, cooled to room temperature, concentrated and purified by chromatography (silica, CH_2Cl_2) to afford the title compound as a colorless solid (820 mg, 38%). $[MNa]^+ = 370$.

[0242] Step D

To a solution of the title compound from Step C above (820 mg) in ^{t}BuOAc (40 mL) was added concentrated H_2SO_4 (0.65 mL). The resulting mixture was stirred at room temperature for 5 h, concentrated, diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated to afford the title compound as a colorless solid (640 mg, 99%). $[M-NH_2]^+ = 231$.

Preparative Example 8

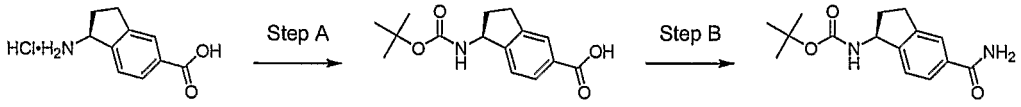


[0243] Step A

To a solution of the title compound from the Preparative Example 3, Step E (153 mg) in EtOH (10 mL) were added NEt_3 (0.16 mL) and hydroxylamine hydrochloride (81 mg). The mixture was heated to reflux for 4 h, then concentrated, dissolved in THF (5 mL) and pyridine (0.19 mL) and cooled to 0°C. Trifluoroacetic anhydride (0.25 mL) was added and the mixture was stirred for 16 h. Concentration and purification by chromatography (silica,

hexanes/EtOAc) afforded the title compound as a white solid (217 mg, >99%). $[MNa]^+ = 392$.

Preparative Example 9



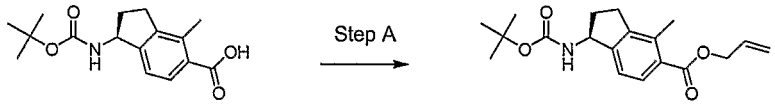
[0244] Step A

To a solution of the title compound from the Preparative Example 4, Step A (33.7 mg) in 1,4-dioxane/H_2O (1:1, 2 mL) were added NaOH (97.4 mg) and di-*tert*-butyl dicarbonate (68.7 mg). The resulting mixture was stirred at room temperature overnight, diluted with EtOAc, washed with 1N aqueous HCl and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated to give a white solid (34.6 mg, 71%). $[MNa]^+ = 300$.

[0245] Step B

To a solution of the title compound from Step A above (34.6 mg) in CH_2Cl_2 (1 mL) were added oxalyl chloride (33 μL) and DMF (2 μL). The mixture was stirred at room temperature for 2 h and concentrated. The remaining residue was dissolved in CH_2Cl_2 (1 mL) and added to a cold (–78°C) saturated solution of NH_3 in CH_2Cl_2 (1 mL). The mixture was stirred at –78°C for 1 h, warmed to room temperature, concentrated, redissolved in CH_2Cl_2 (5 mL), filtered, and concentrated to give a white solid (25.9 mg, 75%). $[MNa]^+ = 299$.

Preparative Example 10

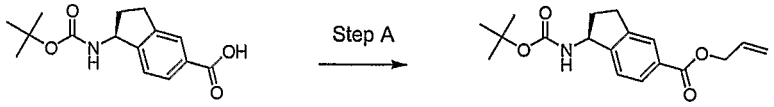


[0246] Step A

To mixture of the title compound from the Preparative Example 7, Step B (536 mg) and allyl bromide (1.6 mL) in $CHCl_3$/THF (1:1, 20 mL) were added Bu_4NHSO_4 (70 mg) and a 1M solution of LiOH in H_2O (10 mL) and the resulting biphasic mixture was stirred at 40°C overnight. The organic phase was separated, concentrated, diluted with $CHCl_3$, washed with

H_2O, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound (610 mg, >99%). $[MNa]^+ = 354$.

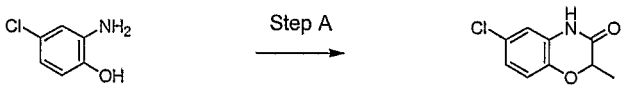
Preparative Example 11



[0247] Step A

To a solution of the title compound from the Preparative Example 9, Step A (97 mg) in dry DMF (5 mL) were added K_2CO_3 (97 mg) and allyl bromide (22 μL). The mixture was stirred overnight, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound (81 mg, 68%). $[MNa]^+ = 340$.

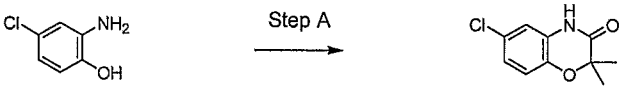
Preparative Example 12



[0248] Step A

To a solution of commercially available 2-amino-4-chloro-phenol (5.0 g) and $NaHCO_3$ (7.7 g) in acetone/H_2O was slowly added 2-bromopropionyl bromide (4 mL) at room temperature, before the mixture was heated to reflux for 3 h. The acetone was evaporated and the formed precipitate was isolated by filtration, washed with H_2O and dried to afford the title compound as brown crystals (6.38 g, 93%). $[MH]^+ = 198$.

Preparative Example 13

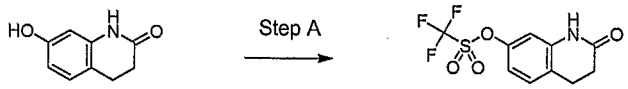


[0249] Step A

To a solution of commercially available 2-amino-4-chloro-phenol (5.0 g) and $NaHCO_3$ (7.7 g) in acetone/H_2O (4:1, 200 mL) was slowly added 2-bromo-

2-methylpropionyl bromide (8.3 mL) at room temperature, before the mixture was heated at ~ 90°C overnight. The acetone was evaporated and the formed precipitate was filtered off, washed with H_2O (100 mL) and recrystallized from acetone/H_2O (1:1) to afford the title compound as a pale brown solid (4.8 g, 33%). $[MH]^+ = 212$.

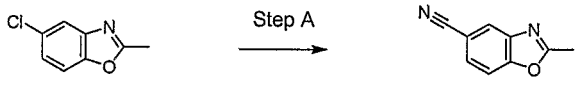
Preparative Example 14



[0250] Step A

To a solution of commercially available 7-hydroxy-3,4-dihydro-1H-quinolin-2-one (1.63 g) in THF (20 mL) was added NaH (95%, 0.28 g). The mixture was stirred at room temperature for 5 min, *N*-phenyl-bis(trifluoromethanesulfonimide) (4.0 g) was added and stirring at room temperature was continued for 2 h. The mixture was cooled to 0°C, diluted with H_2O (40 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (2.29 g, 78%). $[MH]^+ = 296$.

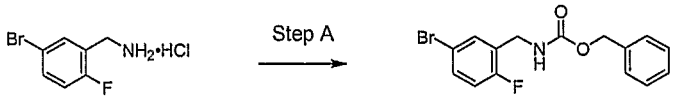
Preparative Example 15



[0251] Step A

Commercially available 5-chloro-2-methylbenzoxazole (1.5 g), KCN (612 mg), dipiperidinomethane (720 μL), $Pd(OAc)_2$ (80 mg) and 1,5-bis-(diphenylphosphino)pentane (315 mg) were dissolved in dry toluene (20 mL), degassed and heated at 160°C in a sealed pressure tube under an argon atmosphere for 24 h. The mixture was diluted with EtOAc, washed subsequently with saturated aqueous NH_4Cl and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound as a colorless solid (372 mg, 26%). ^{1}H-NMR ($CDCl_3$) □= 7.90 (s, 1 H), 7.48-7.58 (s, 2 H), 2.63 (s, 3 H).

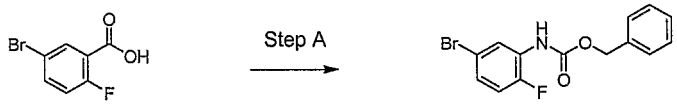
Preparative Example 16



[0252] Step A

A solution of 5-bromo-2-fluorobenzylamine hydrochloride (5.39 g), K_2CO_3 (7.74 g) and benzyl chloroformate (3.8 mL) in THF/H_2O was stirred at room temperature for 90 min. The resulting mixture was concentrated, diluted with EtOAc, washed with 10% aqueous citric acid, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and slurried in pentane. The formed precipitate was collected by filtration to give the title compound as colorless needles (7.74 g, >99%). $[MH]^+ = 338/340$.

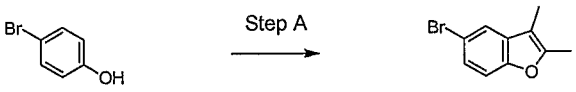
Preparative Example 17



[0253] Step A

To a suspension of commercially available 5-bromo-2-fluoro-benzoic acid (4.52 g) in dry toluene (200 mL) were added NEt_3 (3.37 mL) and diphenylphosphoryl azide (5.28 mL). The resulting clear solution was heated to reflux for 16½ h, then benzyl alcohol (2.51 mL) was added and heating to reflux was continued for 3 h. The mixture was concentrated and purified by flash chromatography (silica, cyclohexane/EtOAc) to afford the title compound (2.96 g, 46%). $[MH]^+ = 324/326$.

Preparative Example 18

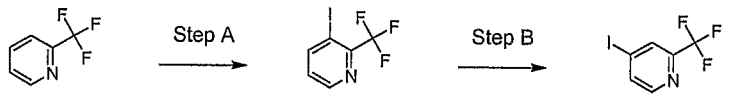


[0254] Step A

A solution of commercially available 4-bromophenol (3.36 g), 3-chloro-butan-2-one (2.2 mL) and K_2CO_3 (4 g) in acetone (40 mL) was heated to reflux for 3 h. Then an additional

amount of 3-chloro-butan-2-one and K_2CO_3 was added and heating to reflux was continued overnight. The mixture was concentrated, dissolved in EtOAc, washed with H_2O, 10% aqueous citric acid and saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated. The obtained colorless oil was added dropwise at 100°C to phosphorous oxychloride (4.7 mL). The resulting mixture was stirred at 100°C for 1 h, cooled to room temperature and ice, followed by EtOAc was added. The organic layer was separated, washed subsequently with saturated aqueous NaCl and saturated aqueous $NaHCO_3$, concentrated and purified by chromatography (silica, cyclohexane) to afford the title compound as a bright yellow solid (2.55 g, 58%). ^{1}H-NMR ($CDCl_3$) □= 7.50 (s, 1 H), 7.20-7.30 (m, 2 H), 2.33 (s, 3 H), 2.10 (s, 3 H).

Preparative Example 19



[0255] Step A

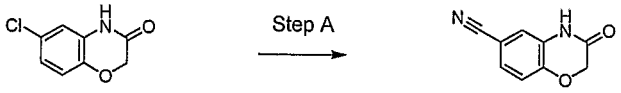
A 2.5M solution of BuLi in hexane (13.6 mL) was diluted in THF (50 mL) and cooled to –78°C (dry ice/acetone). To this solution were subsequently added 2,2,6,6-tetramethylpiperidine (4.8 g) and commercially available 2-(trifluoromethyl)pyridine (5 g). The mixture was stirred at –78°C for 2 h and then a solution of iodine (17.3 g) in THF (50 mL) was added. The cooling bath was removed and the mixture was stirred at room temperature overnight. Then the mixture was quenched with 1M aqueous $Na_2S_2O_3$ (50 mL), the organic phase was separated and the aqueous phase was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, CH_2Cl_2) to afford the title compound as a pale yellow solid (6.3 g, 68%). ^{1}H-NMR ($CDCl_3$) □= 8.63 (dd, 1 H), 8.36 (d, 1 H), 7.20 (dd, 1 H).

[0256] Step B

A 2.5M solution of BuLi in hexane (7.2 mL) was diluted in THF (30 mL) and cooled to –78°C (dry ice/acetone). To this solution were subsequently and dropwise added ^{i}Pr$_2$NH (2.5 mL) and the title compound from Step A above (4.9 g). The mixture was stirred at –78°C for 2 h, quenched at –78°C with MeOH (2 mL), concentrated and purified by

chromatography (silica, cyclohexane/EtOAc) to afford the title compound as yellow needles (1.6 g, 32%). ^{1}H-NMR ($CDCl_3$) □= 8.40 (d, 1 H), 8.06 (s, 1 H), 7.90 (d, 1 H).

Preparative Example 20



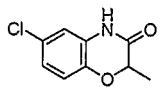
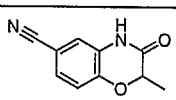
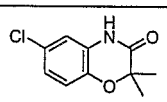
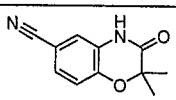
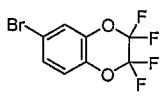
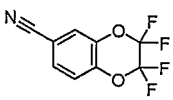
[0257] Step A

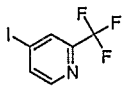
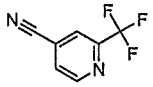
A suspension of commercially available 6-chloro-4*H*-benzo[1,4]oxazin-3-one (3.2 g) and CuCN (2.9 g) in dry *N*-methyl-pyrrolidin-2-one (15 mL) was placed in a preheated oil bath (~250°C). After stirring at this temperature overnight, the mixture was concentrated, diluted with H_2O (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with H_2O (2 x 200 mL) and saturated aqueous NaCl (200 mL), dried ($MgSO_4$), filtered and concentrated. The remaining residue crystallized from EtOAc/toluene to afford the title compound as a tan solid (720 mg, 24%). $[MH]^+ = 175$.

Preparative Examples 21-24

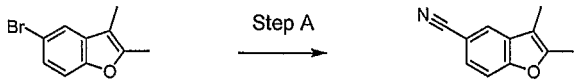
[0258] Following a similar procedure as described in the Preparative Example 20, except using the intermediates indicated in Table I-1 below, the following compounds were prepared.

Table I-1

Prep. Ex. #	intermediate	product	yield
21			39% $[MH]^+ = 189$
22			45% $[MH]^+ = 203$
23			74% ^{1}H-NMR ($CDCl_3$) □= 7.30 (d, 1 H), 7.06 (s, 1 H), 7.03 (d, 1 H).

Prep. Ex. #	intermediate	product	yield
24			64% $[MH]^+ = 173$

Preparative Example 25



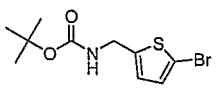
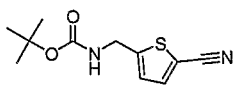
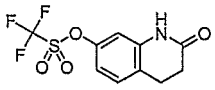
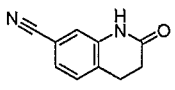
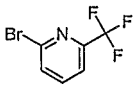
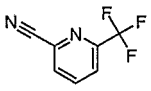
[0259] Step A

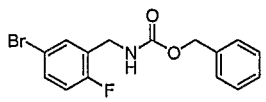
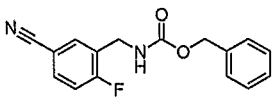
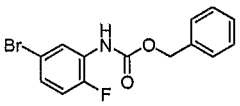
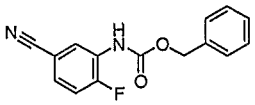
A mixture of the title compound from the Preparative Example 18, Step A (2.55 g), $Zn(CN)_2$ (1.0 g) and $Pd(PPh_3)_4$ (653 mg) in dry DMF (10 mL) was degassed and heated at 85°C under an argon atmosphere for 40 h. The mixture was concentrated, diluted with EtOAc, washed subsequently with 10% aqueous citric acid and saturated aqueous NaCl, dried ($MgSO_4$), concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound as colorless crystals (1.05 g, 54%). ^{1}H-NMR ($CDCl_3$) □= 7.72 (s, 1 H), 7.35-7.50 (m, 2 H), 2.40 (s, 3 H), 2.18 (s, 3 H).

Preparative Examples 26-30

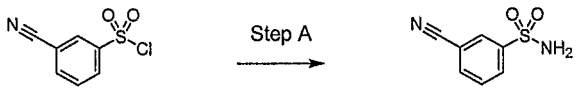
[0260] Following a similar procedure as described in the Preparative Example 25, except using the intermediates indicated in Table I-2 below, the following compounds were prepared.

Table I-2

Prep. Ex. #	intermediate	product	yield
26			>99% $[MNa]^+ = 261$
27			94% $[MH]^+ = 173$
28			86% $[MH]^+ = 173$

Prep. Ex. #	intermediate	product	yield
29			98% ^{1}H-NMR ($CDCl_3$) □= 7.10-7.75 (m, 8 H), 5.22 (br s, 1 H), 5.13 (s, 2 H), 4.42 (d, 2 H).
30			56% $[MH]^+ = 271$

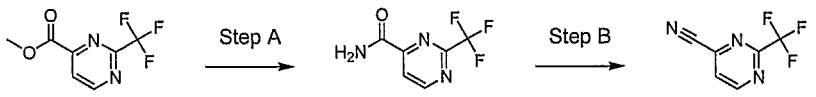
Preparative Example 31



[0261] Step A

A solution of commercially available 3-cyano-benzenesulfonyl chloride (1.07 g) in a 33% solution of NH_3 in H_2O (40 mL) was stirred at room temperature for 1 h, then concentrated to ~ 20 mL and placed in an ice bath. The formed precipitate was separated by filtration, washed with H_2O and dried in vacuo to afford the title compound as a colorless solid (722 mg, 75%). $[MH]^+ = 183$.

Preparative Example 32



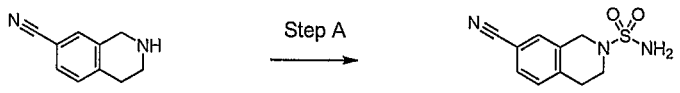
[0262] Step A

Commercially available 2-trifluoromethyl-pyrimidine-4-carboxylic acid methyl ester (1.0 g) was dissolved in a 7M solution of NH_3 in MeOH and heated in a sealed pressure tube to 50°C for 16 h. Cooling to room temperature and concentration afforded the title compound (941 mg, >99%). $[MH]^+ = 192$.

[0263] Step B

A 2M solution of oxalyl chloride in CH_2Cl_2 (520 μL) was diluted in DMF (3 mL) and then cooled to 0°C. Pyridine (168 μL) and a solution of the title compound from Step A above (100 mg) in DMF (1 mL) were added and the mixture was stirred at 0°C for 3 h and then at room temperature overnight. The mixture was concentrated, diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated to afford the title compound (60 mg, 65%). ^{1}H-NMR ($CDCl_3$) □= 9.20 (d, 1 H), 7.85 (d, 1 H).

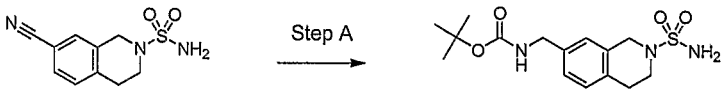
Preparative Example 33



[0264] Step A

A solution of commercially available 7-cyano-1,2,3,4-tetrahydroisoquinoline (103 mg) and sulfamide (69 mg) in dry 1,2-dimethoxyethane (10 mL) was heated to reflux overnight, concentrated, diluted with EtOAc, washed subsequently with 10% aqueous citric acid and saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated to give the title compound as a colorless solid (165 mg, >99%). $[MH]^+ = 238$.

Preparative Example 34

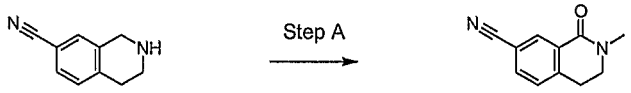


[0265] Step A

To an ice cooled solution of the title compound from the Preparative Example 33, Step A (165 mg) in dry MeOH (20 mL) were added di-*tert*-butyl dicarbonate (300 mg) and $NiCl_2 \cdot 6H_2O$ (20 mg), followed by the careful portionwise addition of $NaBH_4$ (220 mg). The resulting black mixture was stirred for 20 min at 0-5°C (ice bath), then the ice bath was removed and stirring at room temperature was continued overnight. Then diethylenetriamine was added and the mixture was concentrated to dryness. The remaining residue was suspended in EtOAc washed subsequently with 10% aqueous citric acid, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by

chromatography (silica, cyclohexane/EtOAc) to afford the title compound as a colorless solid (109 mg, 46%). $[MNa]^+ = 364$.

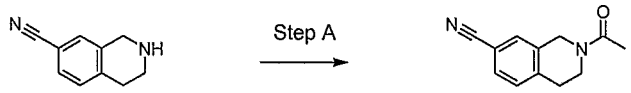
Preparative Example 35



[0266] Step A

A solution of commercially available 7-cyano-1,2,3,4-tetrahydroisoquinoline (407 mg) in dry CH_2Cl_2 (10 mL) was added iodosobenzene (1.13 g). The reaction mixture was stirred at room temperature overnight, diluted with CH_2Cl_2, washed subsequently with 10% aqueous citric acid and saturated aqueous NaCl, dried ($MgSO_4$), filtered, absorbed on silica and purified by chromatography (silica, CH_2Cl_2/MeOH). The obtained intermediate (240 mg) was dissolved in dry DMF (7 mL) and cooled to 0°C. An excess of NaH and methyl iodide were added subsequently and the mixture was stirred for 2 h while warming to room temperature. The mixture was diluted with EtOAc, washed subsequently with 1N aqueous HCl and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to give the title compound as a slowly crystallizing oil (104 mg, 22%). $[MH]^+ = 187$.

Preparative Example 36



[0267] Step A

To a solution of commercially available 7-Cyano-1,2,3,4-tetrahydroisoquinoline (158 mg) in acetic anhydride (5 mL) was added pyridine (0.2 mL). The mixture was stirred overnight and then concentrated to afford the crude title compound. $[MNa]^+ = 223$.

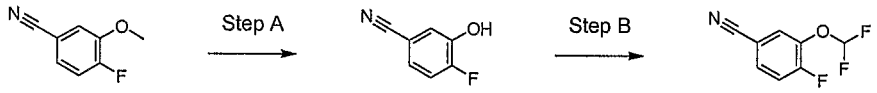
Preparative Example 37



[0268] Step A

The title compound from the Preparative Example 20, Step A (549 mg) was dissolved in dry DMF (7 mL) and cooled to 0°C. An excess of NaH and methyl iodide were added subsequently and the mixture was stirred for 2 h while warming to room temperature. The mixture was diluted with EtOAc, washed subsequently with 1N aqueous HCl and saturated aqueous NaCl, dried ($MgSO_4$), filtered, absorbed on silica and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound as colorless needles (311 mg, 52%). $[MH]^+ = 189$.

Preparative Example 38



[0269] Step A

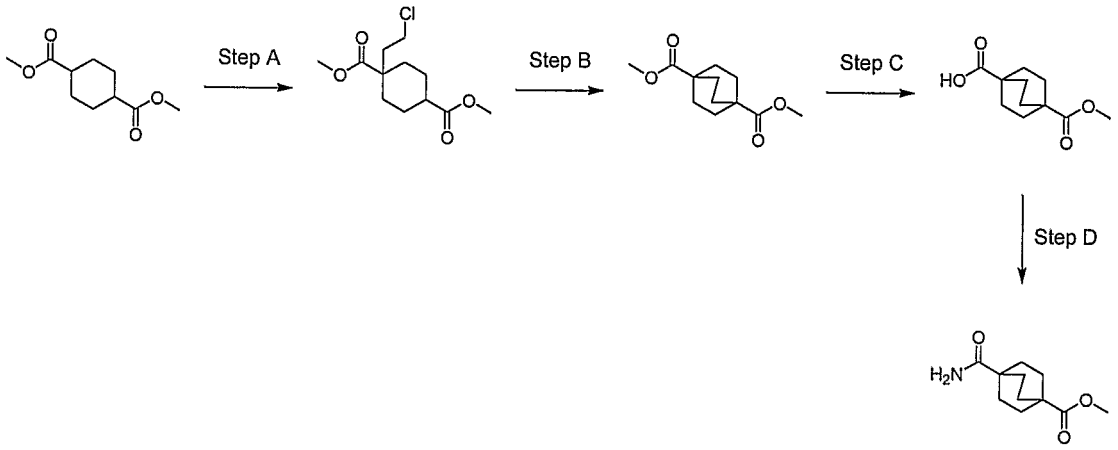
Under an argon atmosphere a mixture of commercially available 4-fluoro-3-methoxybenzonitrile (5.0 g), $AlCl_3$ (8.8 g) and NaCl (1.94 g) was heated (melted) to 190°C for 45 min, cooled, poured on ice (200 mL) and extracted with $CHCl_3$ (3 x). The combined organic phases were washed with H_2O, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound as colorless needles (3.45 g, 76%). $[MH]^+ = 138$.

[0270] Step B

A suspension of the title compound from Step A above (883 mg) and K_2CO_3 (980 mg) in dry DMF (15 mL) was heated to 50°C for 10 min and then cooled to –40°C. Chlorodifluoromethane (50 g) was condensed into the mixture and the resulting slurry was stirred at 80°C with a dry ice condenser for 6 h and then at room temperature overnight without condenser. The mixture was concentrated, diluted with EtOAc, washed subsequently with 1N aqueous HCl and saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated.

Purification by chromatography (silica, cyclohexane/EtOAc) afforded the crude title compound as a colorless oil (1.31 g). $[MH]^+ = 188$.

Preparative Example 39



[0271] Step A

To a cooled (–30°C) solution of $^iPr_2NH$ (16.9 mL) in THF (140 mL) was dropwise added a 2.5M solution of BuLi in hexane (43.2 mL). The mixture was stirred between –20°C and –30°C for 20 min and then cooled to –78°C. To this solution dry HMPA (72 mL) was added dropwise not allowing the temperature of the mixture to exceed –70°C. The resultant mixture was cooled again to –78°C and a solution of commercially available dimethylcyclohexane-1,4-dicarboxylate (20 g) in THF (20 mL) was added dropwise over a period of ~10 min. Stirring at –78°C was continued for 40 min, then 1-bromo-2-chloroethane (10 mL) was added over a period of 5 min, the cooling bath was removed and the mixture was allowed to warm to room temperature. The mixture was then quenched with saturated aqueous NH_4Cl, the volatiles were removed by evaporation and the mixture was diluted with cyclohexane and H_2O. The aqueous phase was separated and extracted with cyclohexane (2x). The combined organic phases were washed with H_2O and saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated. The remaining residue was distilled (10^{-2} mbar, 100°C) to give the title compound as a pale yellow oil (17 g, 65%). $[MH]^+ = 263$.

[0272] Step B

To a cooled (–30°C) solution of $^{i}Pr_2NH$ (18.7 mL) in THF (180 mL) was dropwise added a 2.5M solution of BuLi in hexane (53.6 mL). The mixture was stirred between –20°C and –30°C for 20 min and then cooled to –78°C. This solution was canulated over a period of 30 min into a cooled (–78°C) mixture of the title compound from Step A above (32 g) and HMPA (90 mL) in THF (440 mL) not allowing the temperature of the mixture to exceed –70°C. Stirring at –78°C was continued for 25 min and then the mixture was allowed to warm to room temperature over a period of 1½ h. The mixture was kept at room temperature for 1 h and then quenched with saturated aqueous NH_4Cl. The volatiles were removed by evaporation and the mixture was diluted with cyclohexane and H_2O. The aqueous phase was separated and extracted with cyclohexane (3 x). The combined organic phases were washed with H_2O and saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated. The remaining residue was recrystallized from cyclohexane to give the title compound (13.8 g, 50%). $[MH]^+ = 227$.

[0273] Step C

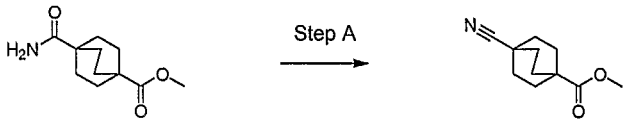
A mixture of the title compound from Step B above (20 g) and KOH (5.5 g) in MeOH/H_2O (10:1, 106 mL) was heated to reflux overnight, cooled to room temperature and concentrated. The residue was diluted with EtOAc and extracted with 1N aqueous NaOH (2 x 100 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated to give the starting material as a white solid. The combined aqueous phases were adjusted with 2N aqueous HCl to pH 1-2 and extracted with EtOAc (4 x 250 mL). The combined turbid organic phases were filtered through a fluted filter, washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated to give the title compound as a colorless solid (13.1 g, 70%). $[MH]^+ = 213$.

[0274] Step D

To a cooled (–40°C) solution of the title compound from Step C above (500 mg) and NEt_3 (1.23 mL) in THF (50 mL) was slowly added ethyl chloroformate (0.67 mL). The mixture was allowed to warm to –25°C and stirred at this temperature for 1 h. A 7N solution of NH_3 in MeOH (10 mL) was added and the mixture was stirred at –20°C for 30 min. The cooling bath was removed and the mixture was stirred at room temperature for 15 min before it was concentrated. To the remaining residue were added H_2O (10 mL) and CH_2Cl_2 (20 mL),

the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were washed with 1N aqueous KOH (10 mL), dried ($MgSO_4$), filtered and concentrated to afford the title compound (458 mg, 92%). $[MH]^+ = 212$.

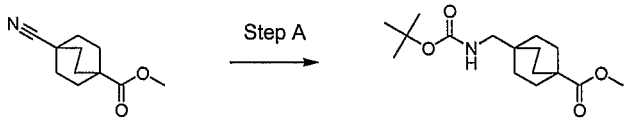
Preparative Example 40



[0275] Step A

To a cooled (0°C) mixture of the title compound from the Preparative Example 39, Step A (228 mg) and imidazole (147 mg) in pyridine (10 mL) was slowly added $POCl_3$ (0.40 mL). The mixture was stirred at 0°C for 1 h and then added to a mixture of ice, NaCl and EtOAc. The organic phase was separated and washed with 1N aqueous HCl until the aqueous phase remained acidic. Drying ($MgSO_4$), filtration and concentration afforded the title compound (137 mg, 72%). $[MH]^+ = 194$.

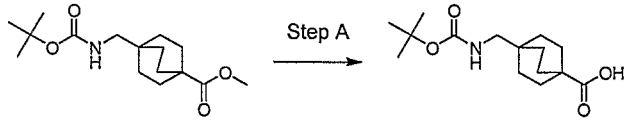
Preparative Example 41



[0276] Step A

The title compound from the Preparative Example 40, Step A (137 mg) was treated similarly as described in the Preparative Example 34, Step A to afford the title compound (163 mg, 77%). $[MNa]^+ = 320$.

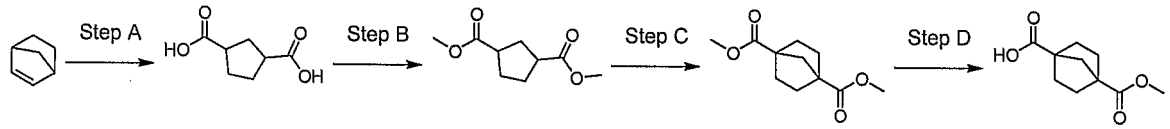
Preparative Example 42



[0277] Step A

To a solution of the title compound from the Preparative Example 41, Step A (2.0 g) in MeOH (10 mL) was added a solution of KOH (753 mg) in H_2O (2 mL). The mixture was heated to reflux for 15 h, concentrated to approximately half of its volume and diluted with H_2O (50 mL). EtOAc (100 mL) was added and the organic phase was separated. The aqueous phase was acidified to pH 4.5 and extracted with EtOAc (3 x 40 mL). The combined organic phases were washed with saturated aqueous NaCl (50 mL), dried ($MgSO_4$), filtered and concentrated to afford the title compound (1.1 g, 56%). $[MNa]^+ = 306$.

Preparative Example 43



[0278] Step A

A mixture of commercially available norbonene (15 g) and $RuCl_3$ (0.3 g) in $CHCl_3$ (100 mL) was stirred at room temperature for 5 min. Then a solution of $NaIO_4$ (163 g) in H_2O (1200 mL) was added and the mixture was stirred at room temperature for 2 d. The mixture was filtered through a pad of celite® and the organic phase was separated. The aqueous phase was saturated with NaCl and extracted with EtOAc (3 x 500 mL). The combined organic phases were treated with $MgSO_4$ and charcoal, filtered and concentrated to afford the crude title compound as thick slightly purple liquid (13.5 g, 53%). $[MH]^+ = 159$.

[0279] Step B

To a solution of the title compound from Step A above (11.2 g) in MeOH (250 mL) was added concentrated H_2SO_4 (0.5 mL) at room temperature. The mixture was heated to reflux for 15 h, cooled to room temperature, filtrated and concentrated. The remaining residue was diluted with EtOAc (100 mL), washed with saturated aqueous $NaHCO_3$ (3 x 50 mL) and saturated aqueous NaCl (50 mL), dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound as a colorless solid (8.43 g, 64%). $[MH]^+ = 187$.

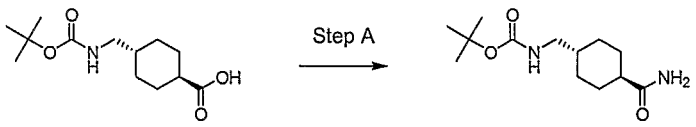
[0280] Step C

To a cooled (–20°C) solution of $^{i}Pr_2NH$ (17.3 mL) in THF (230 mL) was dropwise added a 2.5M solution of BuLi in hexane (45.3 mL). The mixture was stirred between –20°C and –30°C for 20 min and then cooled to –78°C. To this solution dry HMPA (63.2 mL) was added dropwise not allowing the temperature of the mixture to exceed –70°C. The resultant mixture was cooled again to –78°C and a solution of the title compound from Step B above (8.43 g) in THF (40 mL) was added dropwise over a period of 20 min. Then the mixture was stirred at 0°C for 20 min and cooled again to –78°C. 1-Bromo-2-chloroethane (6.32 mL) was added over a period of 40 min, the cooling bath was removed and the mixture was allowed to warm to room temperature over a period of 2 h. The mixture was then quenched with saturated aqueous NH_4Cl (60 mL), concentrated to $^1/_5$ volume and diluted with H_2O (120 mL). The aqueous phase was separated and extracted with cyclohexane (3 x100 mL). The combined organic phases were washed with H_2O (100 mL) and saturated aqueous NaCl (100 mL), dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound as a colorless solid (7.86 g, 82%). $[MH]^+ = 213$.

[0281] Step D

To a solution of the title compound from Step C above (3.5 g) in MeOH (15 mL) was added a solution of KOH (1.6 g) in H_2O (1.75 mL). Using a microwave, the mixture was heated to 140°C for 25 min before H_2O (30 mL) was added. The aqueous mixture was washed with cyclohexane (2 x 30 mL), adjusted to pH 1 with 1N aqueous HCl and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were washed with saturated aqueous NaCl (15 mL), dried ($MgSO_4$), filtered, concentrated and purified by flash chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (2.3 g, 70%). $[MH]^+ = 199$.

Preparative Example 44



[0282] Step A

To a solution of commercially available *trans*-4-(*tert*-butoxycarbonylamino-methyl)-cyclohexanecarboxylic acid (262 mg) in dry THF (5 mL) was added 1,1'-carbonyldiimidazole (243 mg). The resulting clear colorless solution was stirred at room temperature for 1 h, then a 0.5M solution of NH_3 in 1,4-dioxane (20 mL) was added and stirring at room temperature was continued for 5 h. The mixture was concentrated and purified by flash chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (250 mg, 97%). $[MNa]^+ = 279$.

Preparative Example 45



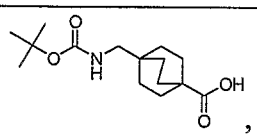
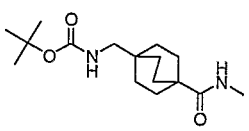
[0283] Step A

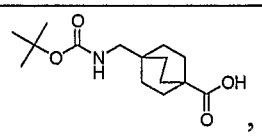
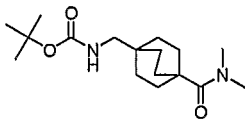
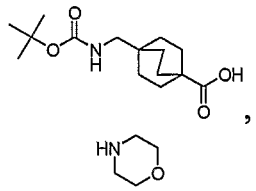
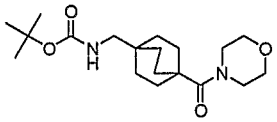
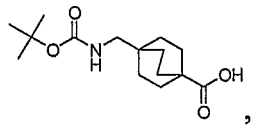
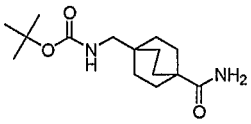
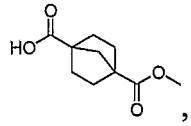
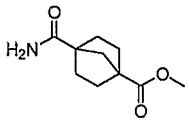
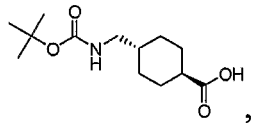
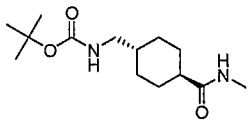
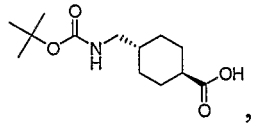
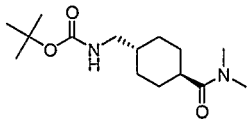
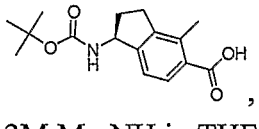
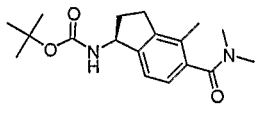
To a solution of title compound from the Preparative Example 7, Step B (35 mg) in DMF (3 mL) were added HATU (60 mg), HOAt (20 mg) and a 2M solution of $MeNH_2$ in THF (150 μL). The mixture was stirred for 16 h, concentrated, diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/acetone) to afford the title compound (35 mg, 95%). $[MH]^+ = 291$.

Preparative Examples 46-53

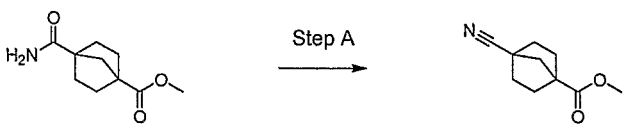
[0284] Following similar procedures as described in the Preparative Examples 39 (method A), 44 (method B) or 45 (method C), except using the acids and amines indicated in Table I-3 below, the following compounds were prepared.

Table I-3

Prep. Ex. #	acid, amine	product	method, yield
46	 , 2M $MeNH_2$ in THF		A, 79% $[MH]^+ = 297$

Prep. Ex. #	acid, amine	product	method, yield
47	 2M Me_2NH in THF		B, 90% $[MH]^+ = 311$
48			B, 44% $[MH]^+ = 353$
49	 7N NH_3 in MeOH		A, 51% $[MH]^+ = 283$
50	 7N NH_3 in MeOH		A, 37% $[MH]^+ = 198$
51	 2M $MeNH_2$ in THF		B, 99% $[MNa]^+ = 293$
52	 2M Me_2NH in THF		B, 98% $[MNa]^+ = 307$
53	 2M Me_2NH in THF		C, 60% $[MH]^+ = 305$

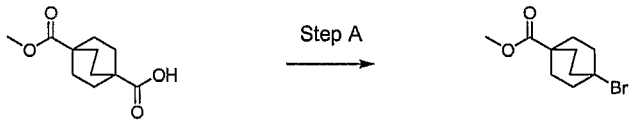
Preparative Example 54



[0285] Step A

The title compound from the Preparative Example 50 (300 mg) was treated similarly as described in the Preparative Example 40, Step A to afford the title compound (250 mg, 92%). $[MH]^+ = 180$.

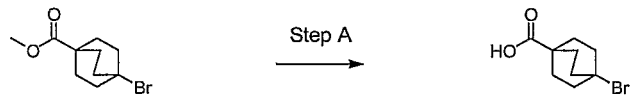
Preparative Example 55



[0286] Step A

To a suspension of the title compound from the Preparative Example 39, Step C (1.0 g) in acetone (7.5 mL) was added phenolphthaleine (1 crystal). To this mixture was added 1M aqueous NaOH until the color of the solution changed to red (pH ~ 8.5). Then a solution of $AgNO_3$ (850 mg) in H_2O (1.25 mL) was added. The formed precipitate (Ag-salt) was collected by filtration, washed with H_2O, acetone and Et_2O and dried in vacuo at room temperature for 6 h and at 100°C for 18 h. The obtained solid (1.28 g) was suspended in hexane (15 mL), bromine (643 mg) was added dropwise and the mixture was stirred at room temperature for 30 min. Then the mixture was placed in a preheated oil bath (80°C) and stirred at the temperature for another 30 min. The mixture was filtered and the filter cake was washed with Et_2O (2 x 30 mL). The combined filtrates were washed with saturated aqueous $NaHCO_3$ (2 x 25 mL), dried ($MgSO_4$), filtered and concentrated to afford the title compound (817 mg, 70%). $[MH]^+ = 247/249$.

Preparative Example 56

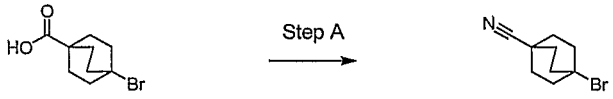


[0287] Step A

To the title compound from the Preparative Example 55, Step A (600 mg) was added 1% aqueous NaOH (65 mL). The mixture was stirred at 100°C (temperature of the oil bath) for 18 h, concentrated to 15 mL and diluted with 1N aqueous HCl (20 mL). The resulting

mixture was acidified to pH 1 with 12N aqueous HCl and extracted with EtOAc (2 x 75 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated to afford the crude title compound, which was not further purified (340 mg, 82%). $[M-CO_2]^+ = 188/190$.

Preparative Example 57



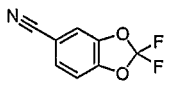
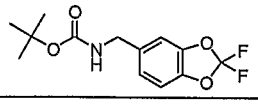
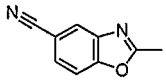
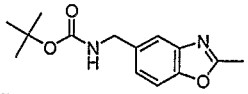
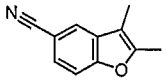
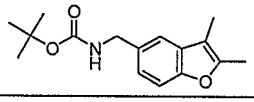
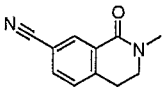
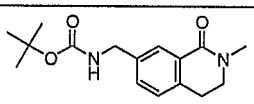
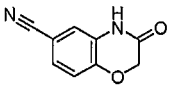
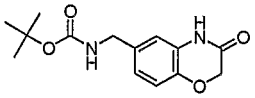
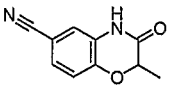
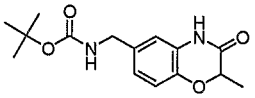
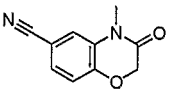
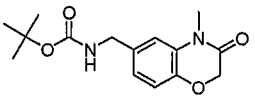
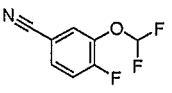
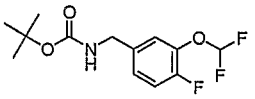
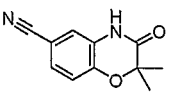
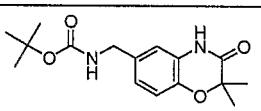
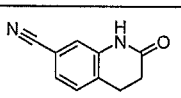
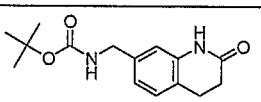
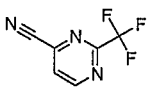
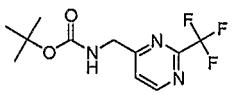
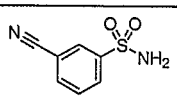
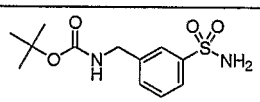
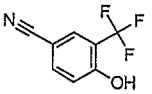
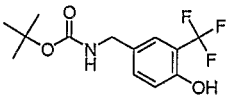
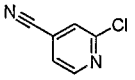
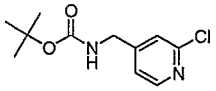
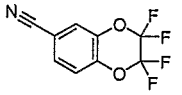
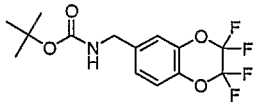
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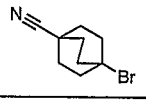
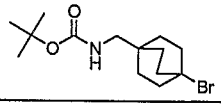
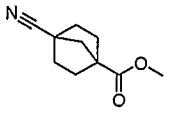
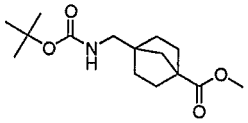
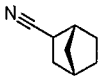
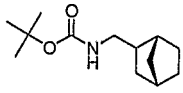
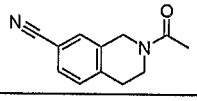
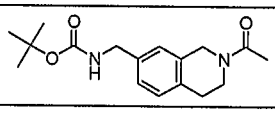
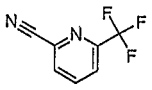
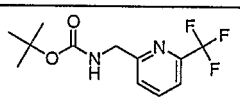
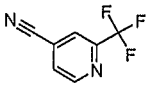
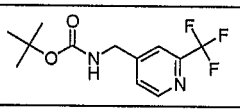
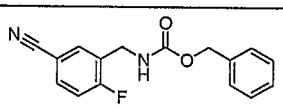
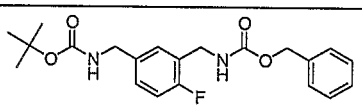
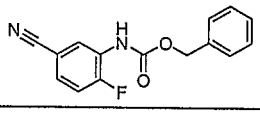
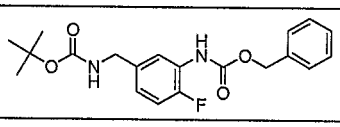
To a cooled (–30°C) solution of the title compound from the Preparative Example 56, Step A (540 mg) and NEt_3 (375 μL) in THF (25 mL) was added ethyl chloroformate (200 μL). The mixture was stirred at –30°C for 1 h and then filtered. The precipitated salts were washed with THF (15 mL). The combined filtrates were cooled to –20°C and a 33% solution of NH_3 in H_2O (7 mL) was added. The mixture was stirred at –20°C for 20 min, then the cooling bath was removed and the mixture was stirred at room temperature for 40 min. Then the mixture was concentrated and dissolved in THF (12 mL). Pyridine (690 μL) was added and the mixture was cooled to 0°C. Trifluoroacetic anhydride (600 μL) was added and the mixture was stirred at 0°C for 2 h. Then the mixture was concentrated to 5 mL, diluted with MeOH (10 mL) and 10% aqueous K_2CO_3 (5 mL) and stirred at room temperature for 2½ h. The MeOH was evaporated and Et_2O/EtOAc (9:1, 80 mL), H_2O (10 mL), saturated aqueous NaCl (10 mL) and saturated aqueous NH_4Cl (15 mL) were added. The organic phase was separated, washed with 0.1N aqueous HCl (30 mL), dried ($MgSO_4$), filtered and concentrated to afford the crude title compound, which was not further purified (222 mg, 86%). $[MH]^+ = 214/216$.

Preparative Examples 58-80

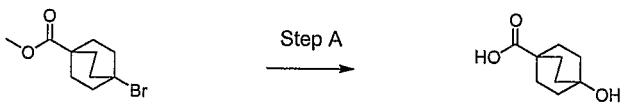
[0289] Following a similar procedure as described in the Preparative Example 34, except using the nitriles indicated in Table I-4 below, the following compounds were prepared.

Table I-4

Prep. Ex. #	nitrile	product	yield
58			68% $[MNa]^+ = 310$
59			73% $[MNa]^+ = 285$
60			68% $[MNa]^+ = 298$
61			69% $[MNa]^+ = 313$
62			41% $[MNa]^+ = 301$
63			51% $[MNa]^+ = 315$
64			62% $[MNa]^+ = 315$
65			n.d. $[MNa]^+ = 314$
66			98% $[MH]^+ = 307$
67			67% $[MH]^+ = 277$
68			18% ^{1}H-NMR ($CDCl_3$) □= 8.80 (d, 1 H), 7.50 (d, 1 H), 5.40 (br s, 1 H), 4.50 (br d, 2 H), 1.40 (s, 9 H)
69			n.d. $[MNa]^+ = 309$
70			67% $[MH]^+ = 292$
71			74% $[MH]^+ = 243$
72			38% $[M\text{-isobutene}]^+ = 282$

Prep. Ex. #	nitrile	product	yield
73			24% $[M\text{-isobutene}]^+ = 262$
74			57% $[MH]^+ = 284$
75			61% $[MH]^+ = 226$
76			n.d. $[MNa]^+ = 305$
77			75% $[MNa]^+ = 299$
78			79% $[MH]^+ = 277$
79			>99% $[MNa]^+ = 411$
80			89% $[MNa]^+ = 397$

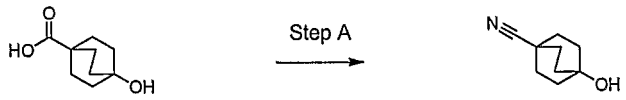
Preparative Example 81



[0290] Step A

To the title compound from the Preparative Example 55, Step A (677 mg) was added 10% aqueous NaOH (65 mL). The mixture was stirred at 100°C (temperature of the oil bath) for 42 h, concentrated to 15 mL and diluted with 1N aqueous HCl (30 mL). The resulting mixture was acidified to pH 1 with 12N aqueous HCl and extracted with EtOAc (5 x 70 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated to afford the title compound (540 mg, 89%). $[MH]^+ = 171$.

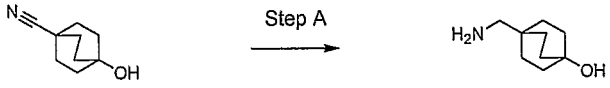
Preparative Example 82



[0291] Step A

To a cooled (–30°C) solution of the title compound from the Preparative Example 81, Step A (540 mg) and NEt_3 (590 μL) in THF (35 mL) was added ethyl chloroformate (320 μL). The mixture was stirred at –30°C for 1 h and then filtered. The precipitated salts were washed with THF (20 mL). The combined filtrates were cooled to –20°C and a 33% solution of NH_3 in H_2O (10 mL) was added. The mixture was stirred at –20°C for 20 min, then the cooling bath was removed and the mixture was stirred at room temperature for 40 min. The mixture was concentrated and dissolved in THF/CH_3CN (4:1, 25 mL). Pyridine (1.26 mL) was added and the mixture was cooled to 0°C. Trifluoroacetic anhydride (1.10 mL) was added and the mixture was stirred at 0°C for 2 h. Then the mixture was concentrated to 5 mL, diluted with MeOH (18 mL) and 10% aqueous K_2CO_3 (9 mL), stirred at room temperature overnight, concentrated to 10 mL, acidified to pH 1 with 1N aqueous HCl and extracted with CH_2Cl_2 (4 x 75 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (433 mg, 90%). $[MH]^+ = 152$.

Preparative Example 83

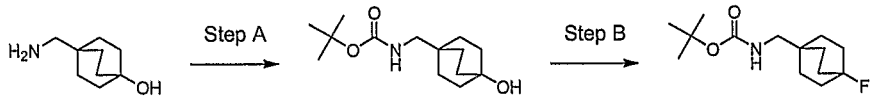


[0292] Step A

To a suspension of $LiAlH_4$ (219 mg) in THF (12 mL) was added a solution of the title compound from the Preparative Example 82, Step A (433 mg) in THF (35 mL) over a period of 20 min. The mixture was heated to reflux for 36 h and then cooled to 0°C. 1N aqueous NaOH (1 mL) was added and the mixture was stirred overnight while warming to room temperature. The mixture was filtered through a pad of celite® and the filter cake was washed

with Et_2O (250 mL). The combined filtrates were concentrated to afford the title compound (410 mg, 92%). $[MH]^+ = 156$.

Preparative Example 84



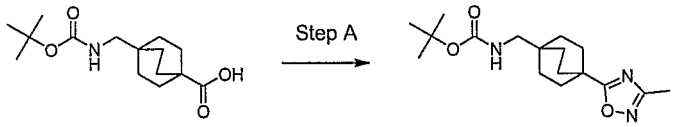
[0293] Step A

To a solution of the title compound from the Preparative Example 83, Step A (390 mg) in THF (80 mL) were successively added $^iPr_2NEt$ (0.66 mL) and di-*tert*-butyl dicarbonate (740 mg). The mixture was stirred at room temperature for 3 d, concentrated, diluted with EtOAc (100 mL), washed subsequently with H_2O (15 mL), 0.1N aqueous HCl and saturated aqueous NaCl, dried ($MgSO_4$), concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (196 mg, 30%). $[MNa]^+ = 278$.

[0294] Step B

To a cooled (–78°C) solution of the title compound from Step A above (85 mg) in CH_2Cl_2 (4 mL) was added a solution of diethylaminosulfur trifluoride (73 μL) in CH_2Cl_2 (4 mL). The mixture was stirred at –78°C for 15 min and then poured on saturated aqueous $NaHCO_3$ (40 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic phases were washed with saturated aqueous NaCl (30 mL), dried over $MgSO_4$, filtered, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound (28 mg, 32%). $[MNa]^+ = 280$.

Preparative Example 85



[0295] Step A

To a solution of the title compound from the Preparative Example 42, Step A (50 mg) in DMF (1.6 mL) were added HATU (67 mg), $^iPr_2NEt$ (68 μL) and *N*-hydroxyacetamidine

(~ 60%, 22 mg). Using a microwave, the mixture was heated in a sealed tube to 130°C for 30 min. Additional HATU (130 mg) and *N*-hydroxyacetamidine (50 mg) were added and the mixture was again heated to 130°C (microwave) for 30 min. Additional HATU (130 mg) and *N*-hydroxyacetamidine (59 mg) were added and the mixture was heated to 140°C (microwave) for 30 min. The mixture was concentrated and purified by flash chromatography (silica, cyclohexane/EtOAc) to afford the title compound (18 mg, 32%). $[MNa]^+ = 322$.

Preparative Example 86



[0296] Step A

To a solution of the title compound from the Preparative Example 49 (150 mg) in THF (6 mL) was added methyl *N*-(triethylammoniosulfonyl) carbamate ["Burgess reagent"] (316 mg). The mixture was stirred at room temperature for 15 h, diluted with EtOAc (15 mL), filtered, concentrated and purified by flash chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (77 mg, 55%). $[MH]^+ = 265$.

Preparative Example 87



[0297] Step A

To a cooled (–40°C) solution of the title compound from the Preparative Example 42, Step A (60 mg) and NEt_3 (40 μL) in THF (5mL) was added ethyl chloroformate (24 μL). The mixture was stirred at –40°C for 1 h and then filtered. The precipitated salts were washed with THF (30 mL). The combined filtrates were cooled to 0°C and a solution of $NaBH_4$ (24 mg) in H_2O (430 μL) was added. The mixture was stirred at 0°C for 1 h, then the cooling bath was removed and the mixture was stirred at room temperature for 1 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous NaCl (5 mL) and

extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (22 mg, 39%). $[MH]^+ = 292$.

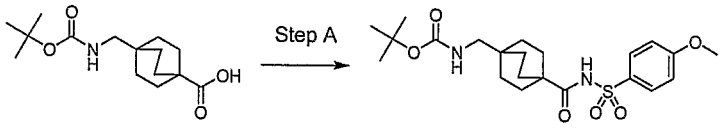
Preparative Example 88



[0298] Step A

To a ice cooled solution of the title compound from the Preparative Example 42, Step A (95 mg) in CH_2Cl_2 (5 mL) were successively added DMAP (61 mg), EDCI (96 mg) and methane sulfonamide (32 mg). The cooling bath was removed and the mixture was stirred at room temperature for 24 h. The mixture was diluted with CH_2Cl_2 (20 mL), washed with 1M aqueous citric acid (15 mL) and saturated aqueous NaCl (15 mL), dried ($MgSO_4$), filtered, concentrated and purified by flash chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (63 mg, 51%). $[MNa]^+ = 383$.

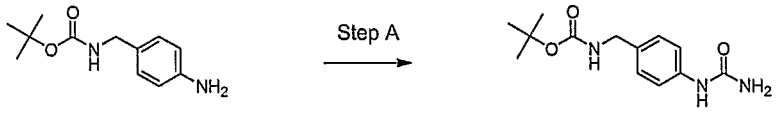
Preparative Example 89



[0299] Step A

The title compound from the Preparative Example 42, Step A (95 mg) was treated similarly as described in the Preparative Example 88, Step A, except using 4-methoxy-phenyl sulfonamide (64 mg) to afford the title compound (58 mg, 38%). $[MH]^+ = 453$.

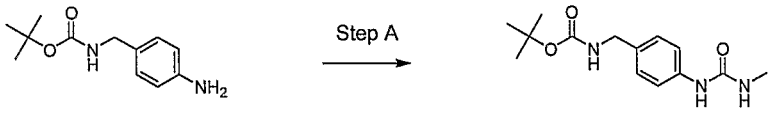
Preparative Example 90



[0300] Step A

To a solution of commercially available (4-amino-benzyl)-carbamic acid *tert*-butyl ester (229 mg) in dry CH_2Cl_2 (1 mL) were successively added ^{i}PrOH (100 μL) and trimethylsilyl isocyanate (154 μL). The resulting reaction mixture was stirred at room temperature for 17½ h. Additional trimethylsilyl isocyanate (154 μL) was added and stirring at room temperature was continued for 75 h. The resulting reaction mixture was diluted with MeOH (5 mL), concentrated and purified by flash chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (263 mg, 99%). $[MH]^+ = 266$.

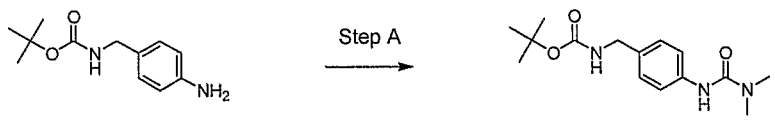
Preparative Example 91



[0301] Step A

To a solution of commercially available (4-amino-benzyl)-carbamic acid *tert*-butyl ester (229 mg) in dry CH_2Cl_2 (1 mL) were successively added $^{i}Pr_2NEt$ (349 μL) and *N*-succinimidyl *N*-methylcarbamate (355 mg). The resulting reaction mixture was stirred at room temperature for 72 h, diluted with EtOAc (20 mL), washed with 0.1M aqueous NaOH (3 x 10 mL), dried ($MgSO_4$), filtered and concentrated to afford the title compound (269 mg, 96%). $[MH]^+ = 280$.

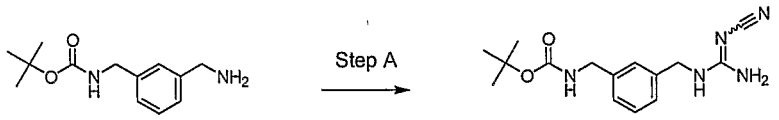
Preparative Example 92



[0302] Step A

To a solution of commercially available (4-amino-benzyl)-carbamic acid *tert*-butyl ester (222 mg) in dry pyridine (1 mL) was added *N,N*-dimethylcarbamoyl chloride (103 μL). The resulting dark red reaction mixture was stirred at room temperature for 17½ h and then diluted with H_2O (10 mL) and EtOAc (20 mL). The organic phase was separated and washed with 1M aqueous NH_4Cl (2 x 10 mL). The aqueous phases were combined and extracted with EtOAc (2 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated to afford the title compound (284 mg, 97%). $[MH]^+ = 294$.

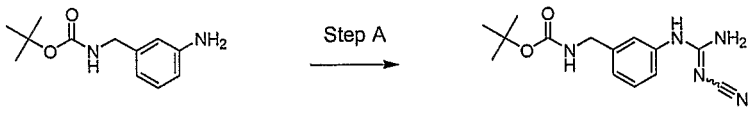
Preparative Example 93



[0303] Step A

To a solution of commercially available (3-aminomethyl-benzyl)-carbamic acid *tert*-butyl ester (236 mg) in DMF (3 mL) was added dimethyl-*N*-cyano-dithioiminocarbonate (146 mg). The mixture was stirred at room temperature overnight, a 7M solution of NH_3 in MeOH (5 mL) and $HgCl_2$ (300 mg) were added and stirring at room temperature was continued for 2 d. Concentration and purification by chromatography (silica, $CHCl_3$/MeOH) afforded the title compound as a white solid (260 mg, 85%). $[MH]^+ = 304$.

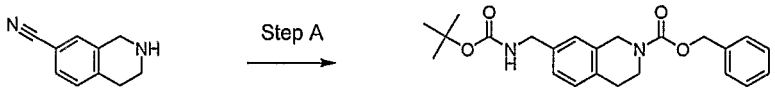
Preparative Example 94



[0304] Step A

To a solution of commercially available (3-amino-benzyl)-carbamic acid *tert*-butyl ester (97 mg) in DMF (5 mL) were added *N*-cyano-methylthioiminocarbonate (50 mg) and $HgCl_2$ (120 mg). The reaction mixture was stirred at room temperature overnight, concentrated and purified by chromatography (silica, $CHCl_3$/MeOH) to afford the title compound as a pale yellow solid (53 mg, 43%). $[MH]^+ = 290$.

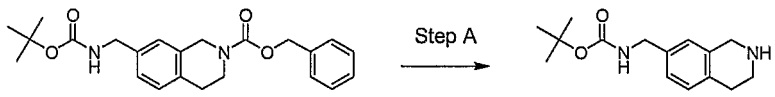
Preparative Example 95



[0305] Step A

A solution of commercially available 7-cyano-1,2,3,4-tetrahydroisoquinoline (2.75 g), K_2CO_3 (3.60 g) and benzylchloroformate (2.7 mL) in THF/H_2O was stirred overnight and then concentrated. The residue was diluted with EtOAc, washed with 10% aqueous citric acid, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$) and concentrated. The residue was dissolved in MeOH (100 mL) and di-*tert*-butyl dicarbonate (7.60 g) and $NiCl_2 \cdot 6H_2O$ (400 mg) was added. The solution was cooled to 0°C and $NaBH_4$ (2.60 g) was added in portions. The mixture was allowed to reach room temperature and then vigorously stirred overnight. After the addition of diethylenetriamine (2 mL) the mixture was concentrated, diluted with EtOAc, washed subsequently with 10% aqueous citric acid, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a colorless oil (1.81 g, 26%). $[MH]^+ = 397$.

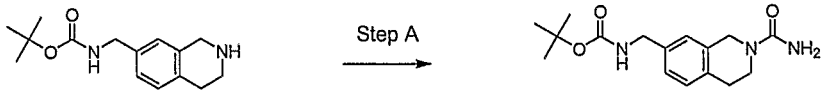
Preparative Example 96



[0306] Step A

A mixture of the title compound from the Preparative Example 95, Step A (1.4 g) and Pd/C (10wt%, 200 mg) in MeOH (40 mL) was hydrogenated at atmospheric pressure overnight, filtered and concentrated to afford the title compound as an off-white solid (960 mg, >99%.) $[MH]^+ = 263$.

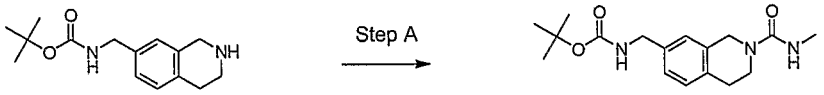
Preparative Example 97



[0307] Step A

To a solution of the title compound from the Preparative Example 96, Step A (100 mg) in dry CH_2Cl_2 (5 mL) were successively added ^iPrOH (500 μL) and trimethylsilyl isocyanate (100 μL). The resulting mixture was stirred at room temperature for 70 h, diluted with MeOH (5 mL), concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a colorless solid (80 mg, 69%). $[MNa]^+ = 328$.

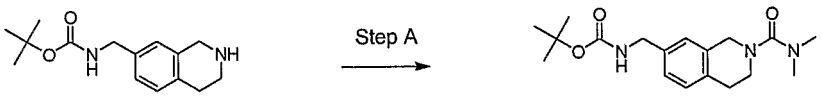
Preparative Example 98



[0308] Step A

To a solution of the title compound from the Preparative Example 96, Step A (100 mg) in dry CH_2Cl_2 (5 mL) were successively added $^iPr_2NEt$ (132 μL) and *N*-succinimidyl *N*-methylcarbamate (131 mg). The resulting mixture was stirred at room temperature for 72 h, diluted with EtOAc (5 mL), washed with 0.1M aqueous NaOH (3 x 10 mL), dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (92 mg, 76%). $[MNa]^+ = 342$.

Preparative Example 99

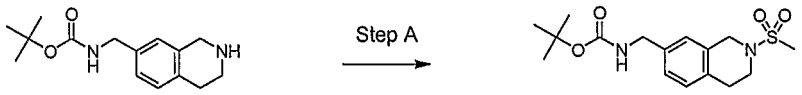


[0309] Step A

To a solution of the title compound from the Preparative Example 96, Step A (100 mg) in dry pyridine (2 mL) was added *N,N*-dimethylcarbamoyl chloride (38 μL). The

resulting mixture was stirred at room temperature for 70 h, diluted with MeOH (5 mL), concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a white solid (40 mg, 32%). $[MNa]^+ = 356$.

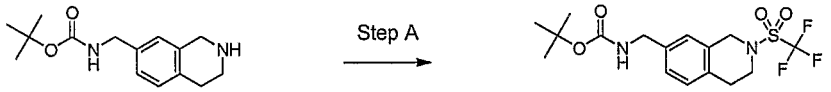
Preparative Example 100



[0310] Step A

To a suspension of the title compound from the Preparative Example 96, Step A (100 mg) and *N*-methylmorpholine (145 μL) in dry CH_2Cl_2/THF (5:1, 12 mL) was added methanesulfonyl chloride (88 μL). The mixture was stirred for 2 h, diluted with CH_2Cl_2, washed subsequently with 10% aqueous citric acid, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound as a colorless solid (96.3 mg, 74%). $[MNa]^+ = 363$.

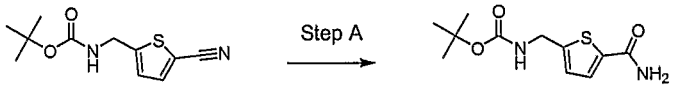
Preparative Example 101



[0311] Step A

To a suspension of the title compound from the Preparative Example 96, Step A (84 mg) and $^iPr_2NEt$ (70 μL) in dry THF (10 mL) was added trifluoromethanesulfonyl chloride (50 μL) at –20°C under an argon atmosphere. The cooling bath was removed and the mixture was stirred for 4 h, diluted with EtOAc, washed subsequently with 10% aqueous citric acid, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound as colorless crystals (47 mg, 37%). $[MNa]^+ = 417$.

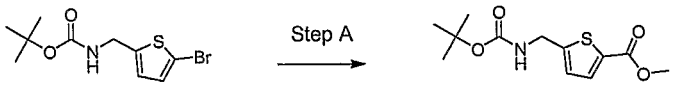
Preparative Example 102



[0312] Step A

To a solution of the title compound from the Preparative Example 26 (242 mg) in MeOH/H_2O (2:1, 30 mL) was added sodium perborate tetrahydrate (470 mg). The mixture was heated to 50°C overnight, concentrated, diluted with EtOAc, washed subsequently with 10% aqueous citric acid and saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated to give the title compound as colorless crystals (220 mg, 85%). $[MNa]^+ = 279$.

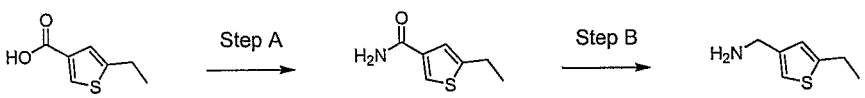
Preparative Example 103



[0313] Step A

Commercially available *tert*-butyl-*N*-[(5-bromo-2-thienyl)methyl]carbamate (2.0 g), $Pd(OAc)_2$ (76 mg), dppp (282 mg) and NEt_3 (2.9 mL) were dissolved in dry DMSO/MeOH (3:1, 60 mL) and stirred at 80°C under a carbon monoxide atmosphere at 7 bar over the weekend. The mixture was concentrated, diluted with EtOAc, washed subsequently with 1N aqueous HCl, H_2O and saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated. Purification by chromatography (silica, cyclohexane/EtOAc) afforded the title compound as colorless crystals (1.73 g, 94%). $[MNa]^+ = 294$.

Preparative Example 104



[0314] Step A

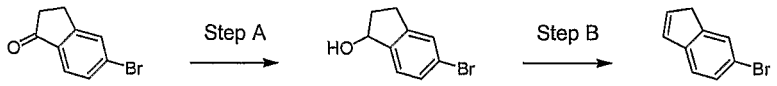
To an ice cooled solution of commercially available 5-ethyl-thiophene-3-carboxylic acid (3.0 g) in CH_2Cl_2 (50 mL) were subsequently added oxalyl chloride (2.3 mL) and DMF (0.4 mL). The mixture was stirred at 0°C for 1 h and then at room temperature for 3 h. The

mixture was concentrated, diluted with CH_2Cl_2 (3 mL) and then slowly added to condensed NH_3 (~30 mL) at ~ –40°C. The resulting mixture was stirred at ~ –30°C for 1 h, slowly warmed to room temperature over a period of ~ 10 h and then concentrated to give the title compound as a tan solid (2.0 g, 68 %). $[MH]^+ = 156$.

[0315] Step B

A vigorously stirred mixture of the title compound from Step A above (1.0 g) and Bu_4NBH_4 (4.9 g) in dry CH_2Cl_2 (30 mL) was heated at 55-62°C for 24 h and then concentrated. The remaining oil was cooled to 0°C and 1N aqueous HCl (15 mL) was slowly added over a period of 1 h. Then the mixture was heated to 100°C for 1 h, cooled to room temperature, washed with Et_2O (100 mL), adjusted to pH ~10 with concentrated aqueous KOH and extracted with Et_2O (100 mL). The organic extract was dried ($MgSO_4$), filtered and concentrated to give the title compound as an oil (0.25 g, 27%). $[MH]^+ = 142$.

Preparative Example 105



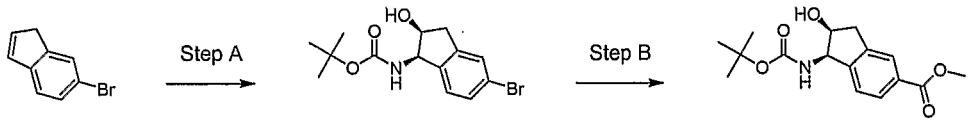
[0316] Step A

To an ice cooled mixture of commercially available 5-bromo-1-indanone (29.84 g) in MeOH (300 mL) was added $NaBH_4$ (2.67 g). After 10 min the mixture was allowed to warm to room temperature. The mixture was stirred for 1½ h and then concentrated. The resulting oil was brought up in EtOAc (300 mL), washed with 1N aqueous NaOH (200 mL) and saturated aqueous NaCl (200 mL), dried ($MgSO_4$), filtered and concentrated to give a white solid (30.11 g, >99%). $[M\text{-}OH]^+ = 195$.

[0317] Step B

A solution of the title compound from Step A above (9.03 g) and 4-toluenesulfonic acid monohydrate (150 mg) in benzene (300 mL) was heated to reflux for 1 h using a Dean Starks trap. Once cooled the reaction solution was washed with H_2O, dried ($MgSO_4$), filtered and concentrated to give a clear oil (7.86 g, 95%). ^{1}H-NMR ($CDCl_3$) □= 7.60 (s, 1 H), 7.40 (dd, J = 8.0, 1.7 Hz, 1 H), 7.26 (d, J = 8.0 Hz, 1 H), 6.83 (dtd, J = 5.7, 2.1, 1.1 Hz, 1 H), 6.55 (dt, J = 5.5, 2.1 Hz, 1 H), 3.39 (br s, 2 H).

Preparative Example 106



[0318] Step A

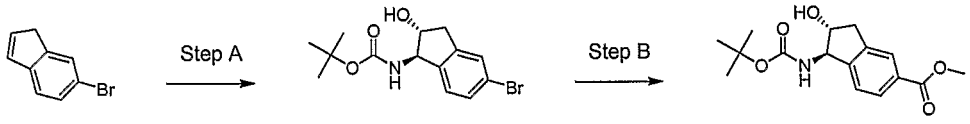
To an ice cooled vigorously stirred mixture of the title compound from the Preparative Example 105, Step B (9.99 g), (*S,S*)-(+)-*N,N'*-bis(3,5-di-*tert*-butyl-salicylindene)-1,2-cyclohexane-diaminomanganese(III) chloride (390 mg) and 4-phenylpyridine *N*-oxide (526 mg) in CH_2Cl_2 (6.2 mL) was added a solution of NaOH (425 mg) in 1.25M aqueous NaClO (53.2 mL) by an addition funnel over 2 ½ h. After the addition was complete, stirring at 0°C was continued for another 3 h. Hexanes (30 mL) was added, the resulting biphasic mixture was filtered through celite® and the filter cake was washed with CH_2Cl_2 (3 x 20 mL). The supernatant was placed in a separatory funnel, the aqueous layer was removed and the organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated. The resulting solid was dissolved in EtOH (100 mL) and a 28% solution of NH_3 in H_2O (200 mL) was added. The solution was stirred at 110°C for 30 min, cooled to room temperature and washed with CH_2Cl_2 (4 x 200 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give a dark brown solid (7.50 g). $[M\text{-}NH_2]^+ = 211$. This solid was dissolved in CH_2Cl_2 (150 mL) and NEt_3 (5.5 mL) and di-*tert*-butyl-dicarbonate (7.87 g) were added subsequently. The resulting solution was stirred for 4 h at room temperature, then absorbed on silica and purified by chromatography (silica, hexanes/EtOAc) to give an off-white solid (6.87 g, 41%). $[MNa]^+ = 350$.

[0319] Step B

A solution of the title compound from Step A above (6.87 g), $Pd(PPh_3)_4$ (1.20 g) in MeOH (100 mL), DMSO (100 mL) and NEt_3 (14 mL) was stirred at 80°C under an atmosphere of carbon monoxide (1 atm) for 18 h. Once the mixture was cooled to room temperature, it was placed in a separatory funnel and EtOAc (200 mL) and 1N aqueous HCl (200 mL) were added. The layers were separated and the aqueous layer was washed with EtOAc (200 mL). The organic layers were combined, washed with 1N aqueous HCl (200 mL), saturated aqueous $NaHCO_3$ (200 mL) and saturated aqueous NaCl (200 mL), dried

($MgSO_4$), filtered and absorbed on silica. Purification by chromatography (silica, hexanes/EtOAc) afforded an off-white solid (1.45 g, 23%). $[MNa]^+ = 330$.

Preparative Example 107



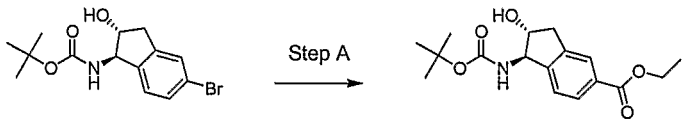
[0320] Step A

To an ice cooled vigorously stirred mixture of the title compound from the Preparative Example 105, Step B (3.92 g), (*R,R*)-(–)-*N,N'*-bis(3,5-di-*tert*-butyl-salicylindene)-1,2-cyclohexane-diaminomanganese(III) chloride (76.2 mg) and 4-phenylpyridine *N*-oxide (103 mg) in CH_2Cl_2 (2.4 mL) was added a solution of NaOH (122 mg) in 1.25M aqueous NaClO (15.3 mL) by an addition funnel over 2 ½ h. After the addition was complete, stirring at 0°C was continued for another 3 h. Hexanes (20 mL) was added, the resulting biphasic mixture was filtered through celite® and the filter cake was washed with CH_2Cl_2 (3 x 20 mL). The supernatant was placed in a separatory funnel, the aqueous layer was removed and the organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated. The remaining brown solid was suspended in CH_3CN (10 mL) at –40°C, trifluoromethane sulfonic acid (1.2 mL) was added and the resulting mixture was stirred at –40 °C for 1½ h. H_2O (20 mL) was added and the mixture was stirred at 110°C for 5 h, while distilling off the CH_3CN. Once the reaction mixture was cooled to room temperature, the aqueous layer was washed with CH_2Cl_2 (2 x 50 mL). The organic layers were discarded and the aqueous layer was basified with 3N aqueous NaOH and washed with EtOAc (3 x 50 mL). The EtOAc phases were combined, dried ($MgSO_4$), filtered and concentrated. $[M\text{-}NH_2]^+ = 211$. The remaining solid residue was dissolved in CH_2Cl_2 (30 mL) and NEt_3 (515 μL) and di-*tert*-butyl-dicarbonate (707 g) were added subsequently. The resulting solution was stirred for 6 h at room temperature, then absorbed on silica and purified by chromatography (silica, hexanes/EtOAc) to give an off-white solid (774 mg, 12%). $[MNa]^+ = 350$.

[0321] Step B

A solution of the title compound from Step A above (774 mg), $Pd(PPh_3)_4$ (136 mg) in MeOH (10 mL), DMSO (10 mL) and NEt_3 (1.6 mL) was stirred at 80°C under an atmosphere of carbon monoxide (1 atm) for 18 h. Once the mixture was cooled to room temperature, it was placed in a separatory funnel and EtOAc (30 mL) and 1N aqueous HCl (30 mL) were added. The layers were separated and the aqueous layer was washed with EtOAc (30 mL). The organic layers were combined, washed with 1N aqueous HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL) and saturated aqueous NaCl (30 mL), dried ($MgSO_4$), filtered and absorbed on silica. Purification by chromatography (silica, hexanes/EtOAc) afforded an off-white solid (333 mg, 46%). $[MNa]^+ = 330$.

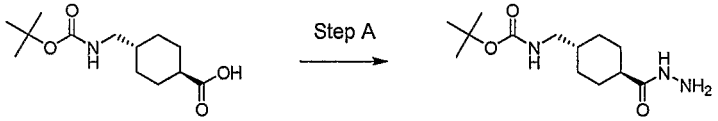
Preparative Example 108



[0322] Step A

The title compound from the Preparative Example 107, Step A above (406 mg) was treated similarly as described in the Preparative Example 107, Step B, except using EtOH (10 mL) as the solvent to afford the title compound (353 mg, 89%). $[MNa]^+ = 344$.

Preparative Example 109

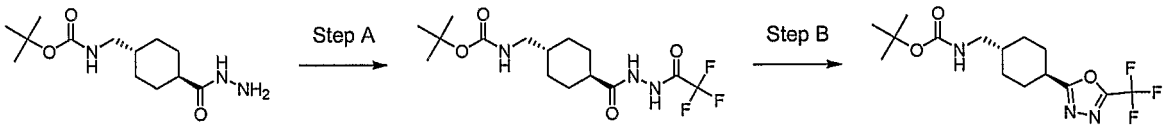


[0323] Step A

To a solution of commercially available *trans*-4-(*tert*-butoxycarbonylamino-methyl)-cyclohexanecarboxylic acid (262 mg) in dry THF (5 mL) was added 1,1'-carbonyldiimidazole (243 mg). The resulting clear colorless solution was stirred at room temperature for 1 h, then hydrazine monohydrate (219 μL) was added and stirring at room temperature was continued for 17 h. The mixture was concentrated and purified by flash chromatography (silica, CH_2Cl_2/MeOH). The isolated white solid was dissolved in EtOAc (50 mL) and washed with

0.01 M aqueous HCl (2 x 50 mL) and saturated aqueous NaCl (50 mL). The combined HCl layers were saturated with NaCl and extracted with EtOAc (2 x 100 mL). The combined EtOAc layers were dried ($MgSO_4$), filtered and concentrated to afford the title compound (264 mg, 97%). $[MNa]^+ = 294$.

Preparative Example 110



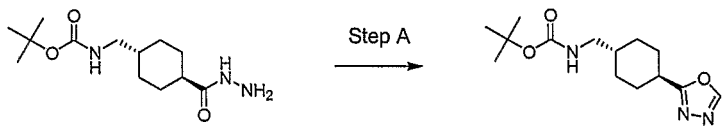
[0324] Step A

To a solution of the title compound from the Preparative Example 109, Step A (136 mg) in dry MeOH (12.5 mL) were successively added trifluoroacetic anhydride (104 μL) and $^iPr_2NEt$ (130 μL). The resulting reaction mixture was stirred at room temperature for 23 h, concentrated and purified by flash chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (66 mg, 43%). $[MNa]^+ = 390$.

[0325] Step B

To a solution of the title compound from Step A above (66 mg) in dry THF (3.6 mL) was added methyl *N*-(triethylammoniosulfonyl) carbamate ["Burgess reagent"] (88 mg). The resulting reaction mixture was heated in a sealed tube to 150°C (microwave) for 15 min, concentrated and purified by flash chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (52 mg, 83%). $[MNa]^+ = 372$.

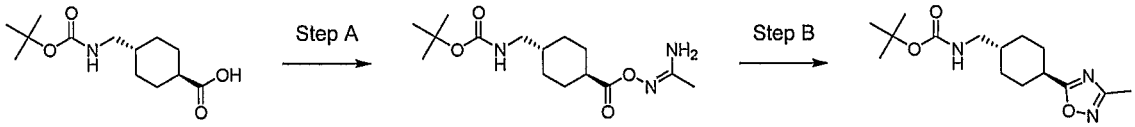
Preparative Example 111



[0326] Step A

To a suspension of the title compound from the Preparative Example 109, Step A (54.3 mg) in trimethyl orthoformate (2 mL) was added dry MeOH (200 μL). The resulting clear solution was heated in a sealed tube to 150°C (microwave) for 24 h, concentrated and purified by flash chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (45.6 mg, 81%). $[MNa]^+ = 304$.

Preparative Example 112



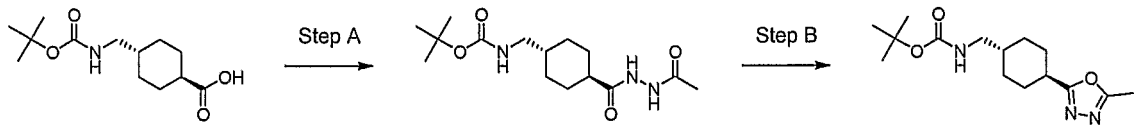
[0327] Step A

To a solution of commercially available *trans*-4-(*tert*-butoxycarbonylamino-methyl)-cyclohexanecarboxylic acid (262 mg) and *N*-hydroxyacetamidine (19 mg) in DMF/CH_2Cl_2 (9:1, 2 mL) were added *N,N'*-diisopropylcarbodiimide (33 mg) and HOBt (36 mg). The resulting mixture was stirred at room temperature for 2 h, concentrated, dissolved in EtOAc, washed subsequently with saturated aqueous $NaHCO_3$, 0.5N aqueous HCl and saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated to afford the title compound (255 mg, 80%). $[MH]^+ = 314$.

[0328] Step B

[0329] To a solution of the title compound from Step A above (55 mg) in EtOH (3 mL) was added a solution of NaOAc (12 mg) in H_2O (270 μL). Using a microwave, the mixture was heated in a sealed vial at 120°C for 50 min. Concentration and purification by chromatography (silica, cyclohexane/EtOAc) afforded the title compound as a colorless oil (24 mg, 46%). $[MH]^+ = 296$.

Preparative Example 113



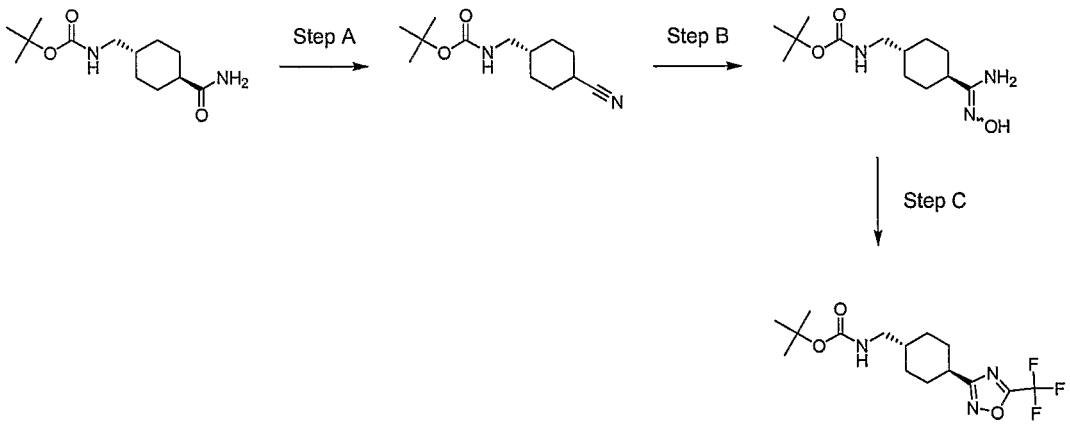
[0330] Step A

To a solution of commercially available *trans*-4-(*tert*-butoxycarbonylamino-methyl)-cyclohexanecarboxylic acid (520 mg) and acetic acid hydrazide (178 mg) in DMF (10 mL) were added *N,N'*-diisopropylcarbodiimide (303 mg) and HOBt (326 mg). The resulting mixture was stirred at room temperature for 2 h, concentrated, dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (400 mg, 64%). $[MH]^+ = 314$.

[0331] Step B

To a solution of the title compound from Step A above (216 mg) in dry THF (10 mL) was added methyl *N*-(triethylammoniosulfonyl) carbamate ["Burgess reagent"] (300 mg). Using a microwave, the mixture was heated in a sealed vial at 150°C for 15 min. Concentration and purification by chromatography (silica, CH_2Cl_2/MeOH) afforded the title compound as a colorless oil (143 mg, 70%). $[MH]^+ = 296$.

Preparative Example 114



[0332] Step A

To a suspension of the title compound from the Preparative Example 44, Step A (552 mg) in dry THF (11 mL) was added methyl *N*-(triethylammoniosulfonyl) carbamate ["Burgess reagent"] (375 mg). The mixture was stirred at room temperature for 30 min, concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a colorless solid (160 mg, 31%). $[MH]^+ = 239$.

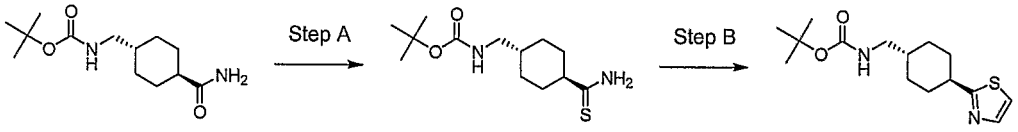
[0333] Step B

To a solution of hydroxylamine hydrochloride in dry MeOH (1 mL) were successively added a 30wt% solution of NaOMe in MeOH (250 μL) and a solution of the title compound from Step A above (160 mg) in dry MeOH (3 mL). The mixture was heated to reflux for 24 h and then concentrated to afford the crude title compound, which was used without further purification (170 mg, 93%). $[MH]^+ = 272$.

[0334] Step C

To a solution of the title compound from Step B above (170 mg) in toluene (5 mL) were successively added $^iPr_2NEt$ (132 μL) and trifluoroacetic anhydride (280 μL). The mixture was heated to reflux for 2½ h, concentrated, dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound (46 mg, 20%). $[MH]^+ = 350$.

Preparative Example 115



[0335] Step A

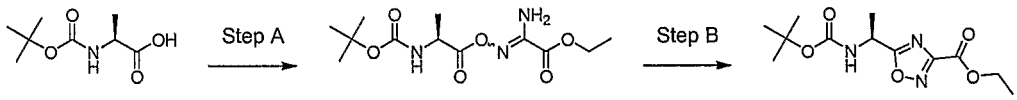
To a suspension of the title compound from the Preparative Example 44, Step A (266 mg) in THF (5 mL) was added 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide ["Lawesson reagent"] (311 mg). The mixture was stirred at room temperature for 1 h, concentrated and purified by chromatography (silica,

CH_2Cl_2/MeOH) to afford the title compound as a pale yellow solid (190 mg, 67%). $[MH]^+ = 273$.

[0336] Step B

To a solution of the title compound from Step A above (190 mg) in DMF (5 mL) were added a 4M solution of HCl in 1,4-dioxane (6 μL) and 2-bromo-1,1-diethoxy-ethane (323 μL). Using a microwave, the mixture was heated in a sealed vial at 100°C for 25 min. The mixture was concentrated, dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound (50 mg, 24%). $[MH]^+ = 297$.

Preparative Example 116



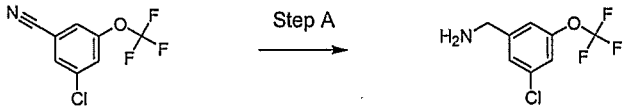
[0337] Step A

To a solution of commercially available *N*-(*tert*-butoxycarbonyl) alanine (227 mg) in DMF (3 mL) were successively added ethyl 2-oximinooxamate (158 mg) and HATU (684 mg). The mixture was stirred at room temperature for 2 h, concentrated, dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$, 1N aqueous HCl and saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated to afford the title compound as a colorless solid (163 mg, 45%). $[MH]^+ = 304$.

[0338] Step B

To a solution of the title compound from Step A above (163 mg) in EtOH (15 mL) was added a solution of NaOAc (78 mg) in H_2O (1 mL). Using a microwave, the mixture was heated in a sealed vial at 120°C for 50 min. Concentration and purification by chromatography (silica, cyclohexane/EtOAc) afforded the title compound as a colorless oil (46 mg, 30%). $[MH]^+ = 286$.

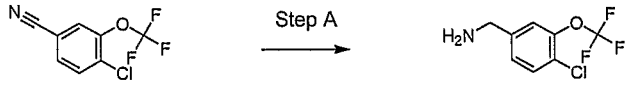
Preparative Example 117



[0339] Step A

A mixture of commercially available 3-chloro-5-trifluoromethoxy-benzonitrile (263 mg) and Bu_4NBH_4 in CH_2Cl_2 (2 mL) was heated to reflux for 12 h. The reaction was quenched with 1M aqueous NaOH, extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and concentrated to afford the title compound. $[MH]^+ = 226$.

Preparative Example 118



[0340] Step A

Commercially available 4-chloro-3-trifluoromethoxy-benzonitrile (227 mg) was treated similarly as described in the Preparative Example 117, Step A to afford the title compound. $[MH]^+ = 226$.

Preparative Example 119



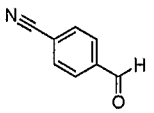
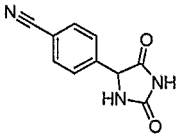
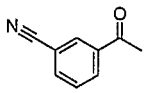
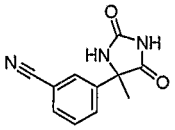
[0341] Step A

A mixture of commercially available 3-cyanobenzaldehyde (263 mg), KCN (130 mg) and $(NH_4)_2CO_3$ (769 mg) in $EtOH/H_2O$ (1:1, 12 mL) was heated to 55°C overnight, cooled, filtered and concentrated. The remaining aqueous mixture was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, hexanes/EtOAc) to give the title compound as a colorless solid (347 mg, 86%). $[MH]^+ = 202$.

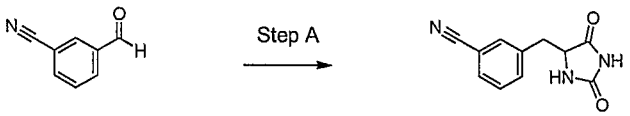
Preparative Examples 120-121

[0342] Following a similar procedure as described in the Preparative Example 119, except using the nitriles indicated in Table I-5 below, the following compounds were prepared.

Table I-5

Prep. Ex. #	protected amine	product	yield
120			90% $[MH]^+ = 202$
121			n.d. $[MH]^+ = 216$

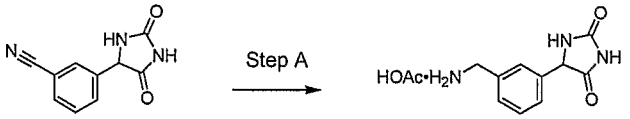
Preparative Example 122



[0343] Step A

A mixture of commercially available 3-cyanobenzaldehyde (262 mg), hydantoin (220 mg) and KOAc (380 mg) in AcOH (2 mL) was heated to reflux for 3 h and then poured on ice (20 g). The colorless precipitate was collected by filtration, washed with ice water and dried to give the title compound as a yellow solid. $[MH]^+ = 216$.

Preparative Example 123



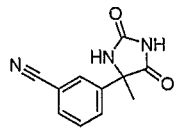
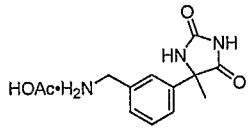
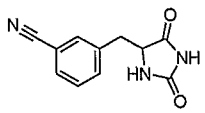
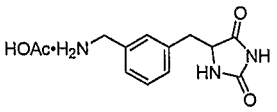
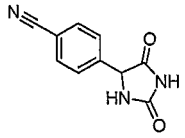
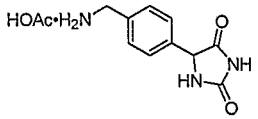
[0344] Step A

A mixture of the title compound from the Preparative Example 119, Step A above (347 mg), 50% aqueous AcOH (2 mL) and Pd/C (10wt%, 200 mg) in EtOH was hydrogenated at 50 psi overnight, filtered and concentrated to give the title compound as colorless solid (458 mg, >99%). $[M\text{-}OAc]^+ = 206$.

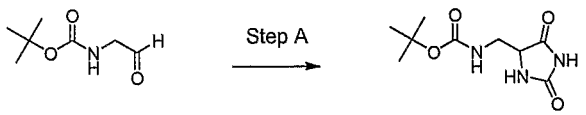
Preparative Examples 124-126

[0345] Following a similar procedure as described in the Preparative Example 123, except using the nitriles indicated in Table I-6 below, the following compounds were prepared.

Table I-6

Prep. Ex. #	protected amine	product	yield MS
124			50% (over 2 steps) $[M\text{-}OAc]^+ = 220$
125			n.d. $[M\text{-}OAc]^+ = 220$
126			76% $[M\text{-}OAc]^+ = 206$

Preparative Example 127

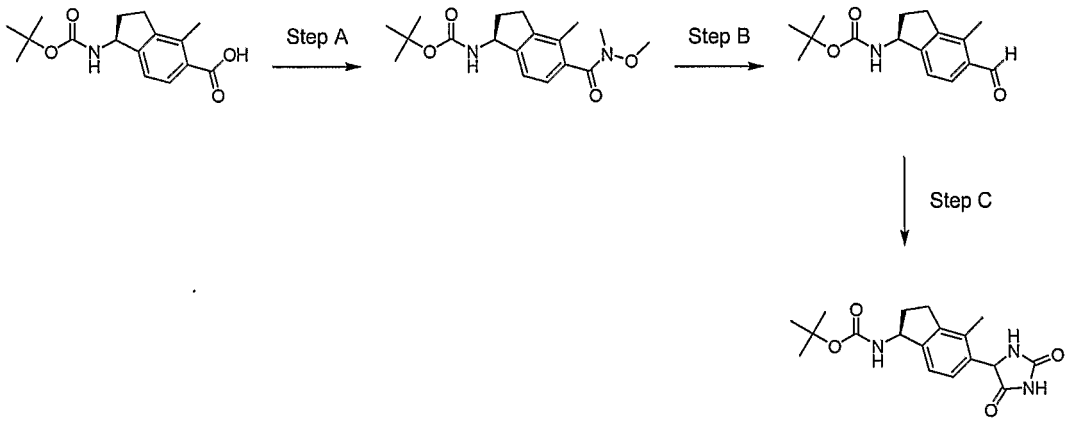


[0346] Step A

To the solution of commercially available 2-*N*-(*tert*-butoxycarbonylamino)acetaldehyde (250 mg) in MeOH/H_2O (1:1, 10 mL) were

added KCN (130 mg) and $(NH_4)_2CO_3$ (650 mg). The mixture was stirred at 55°C overnight, then cooled to room temperature, acidified (pH 2) with 3N aqueous HCl and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated to give a white solid (75 mg, 21%). $[MH]^+ = 230$.

Preparative Example 128



[0347] Step A

To a solution of the title compound from the Preparative Example 7, Step B (100 mg), *N*-methyl-*N*-methoxyamine hydrochloride (42.2 mg) in CH_2Cl_2 (3 mL) and DMF (1 mL) were added EDCI (84.3 mg), HOBt (58 mg) and $NaHCO_3$ (121 mg). The mixture was stirred at room temperature overnight, washed with saturated aqueous Na_2CO_3 (5 mL) and 1N aqueous HCl (5 mL) and concentrated to give the desired product, which was used without further purification (97 mg, 84%). $[MH]^+ = 321$.

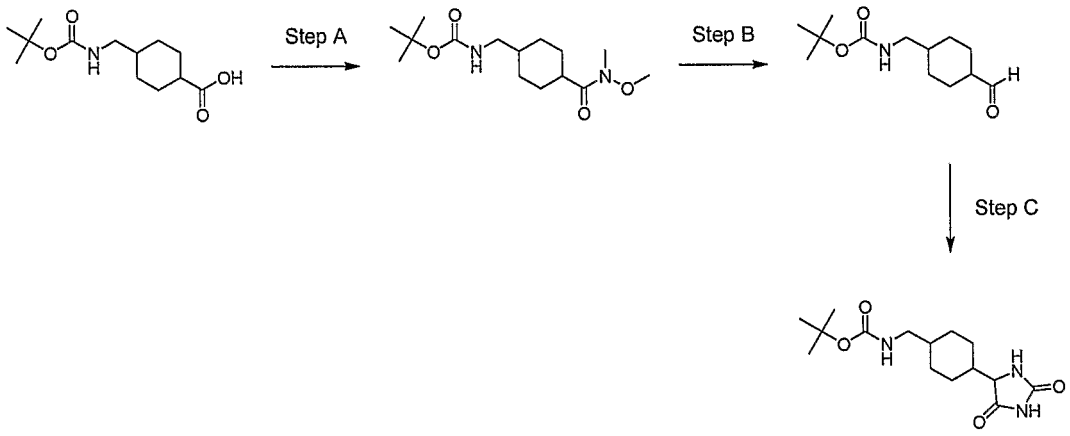
[0348] Step B

To the title compound from Step A above (256 mg) in anhydrous Et_2O (10 mL) was added a 1M solution of $LiAlH_4$ in Et_2O (4 mL). The mixture was stirred for 20 min and then cooled to 0°C. 1M aqueous NaOH (5 mL) was added dropwise, followed by the addition of Et_2O (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with saturated aqueous NaCl (5 mL), dried ($MgSO_4$), concentrated and purified by chromatography (silica, hexanes/EtOAc) to give a white solid (178 mg, 85%). $[MH]^+ = 262$.

[0349] Step C

To the title compound from Step B above (178 mg) in MeOH/H_2O (1:1, 10 mL) were added KCN (67 mg) and $(NH_4)_2CO_3$ (262 mg). The mixture was stirred at 55°C overnight, then cooled to room temperature, acidified (pH 2) with 3N aqueous HCl and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated to give a white solid (170 mg, 73%). $[MH]^+ = 346$.

Preparative Example 129



[0350] Step A

To the solution of commercially available 4-(*tert*-butoxycarbonylamino-methyl)-cyclohexanecarboxylic acid (515 mg), *N*-methyl-*N*-methoxyamine hydrochloride (390 mg) in CH_2Cl_2 (20 mL) were added PyBOP (1.04 g) and NEt_3 (0.84 mL). The mixture was stirred for 2 h at room temperature, washed with saturated aqueous Na_2CO_3 (5 mL) and 1N aqueous HCl (5 mL), concentrated and purified by chromatography (silica, hexanes/EtOAc) to give a white solid (544 mg, 91%). $[MH]^+ = 323$.

[0351] Step B

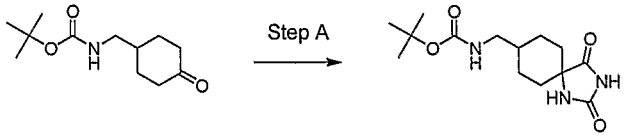
To the title compound from Step A above (544 mg) in anhydrous Et_2O (10 mL) was added a 1M solution of $LiAlH_4$ in Et_2O (1.8 mL). The mixture was stirred for 20 min and then cooled to 0°C. 1M aqueous NaOH (5 mL) was added dropwise, followed by the addition of Et_2O (10 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with saturated aqueous NaCl

(5 mL), dried ($MgSO_4$), concentrated and purified by chromatography (silica, hexanes/EtOAc) to give a white solid (440 mg, >99%). $[MH]^+ = 242$.

[0352] Step C

To the title compound from Step B above (440 mg) in MeOH/H_2O (1:1, 12 mL) was added were added KCN (178 mg) and $(NH_4)_2CO_3$ (670 mg). The mixture was stirred at 55°C overnight, then cooled to room temperature, acidified (pH 2) with 3N aqueous HCl and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated to give a white solid (454 mg, 81%). $[MH]^+ = 312$.

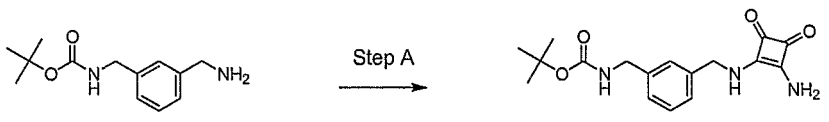
Preparative Example 130



[0353] Step A

To a solution of commercially available 4-*N*-(*tert*-butoxycarbonylamino-methyl)-cyclohexanone (0.26 g) in EtOH/H_2O (1:1, 20 mL) were added NaCN (0.10 g) and $(NH_4)_2CO_3$ (0.56 g). The resulting mixture was heated to reflux overnight, partially concentrated, diluted with H_2O and filtered to give a white solid (0.19 g, 56%). $[MNa]^+ = 320$.

Preparative Example 131

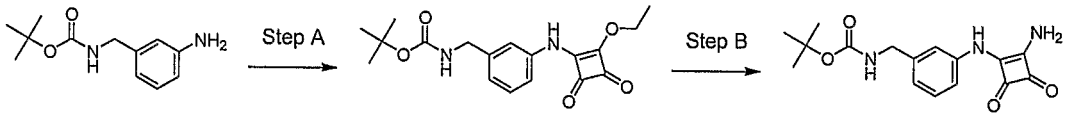


[0354] Step A

To a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (1.3 mL) in EtOH (40 mL) was added commercially available (3-aminomethyl-benzyl)-carbamic acid *tert*-butyl ester (1.39 g). The mixture was stirred for 2 h, a 28% solution of NH_3 in H_2O (40 mL) was added

and stirring was continued for 2 h. Then the mixture was concentrated and slurried in MeOH (20 mL). The formed precipitate was collected by filtration to give the title compound (1.6 g, 82%). $[MNa]^+ = 354$.

Preparative Example 132



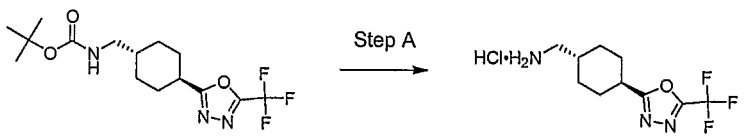
[0355] Step A

To a solution of commercially available (3-amino-benzyl)-carbamic acid *tert*-butyl ester (1.11 g) in EtOH (20 mL) was added 3,4-diethoxy-3-cyclobutene-1,2-dione (1.30 g). The mixture was heated to reflux for 2½ h, cooled to room temperature filtered and concentrated. The remaining solid residue was crystallized from refluxing EtOH to afford the title compound (687 mg, 40%). $[MNa]^+ = 369$.

[0356] Step B

The title compound from Step A above (346 mg) was dissolved in a ~7N solution of NH_3 in MeOH (14.3 mL). The reaction mixture was stirred at room temperature for 3 h and then concentrated to afford the title compound (316 mg, >99%). $[MNa]^+ = 340$.

Preparative Example 133



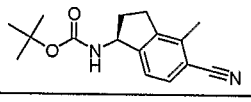
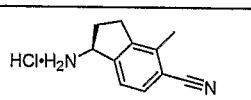
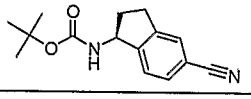
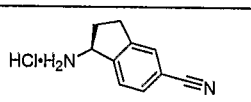
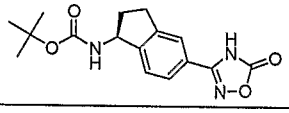
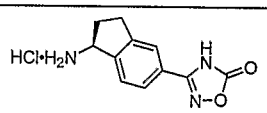
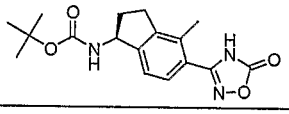
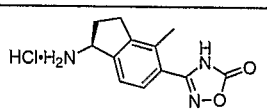
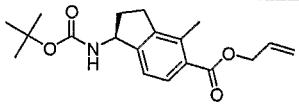
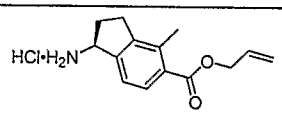
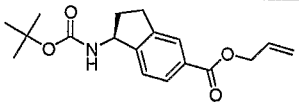
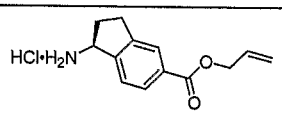
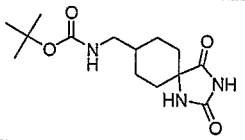
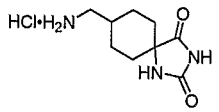
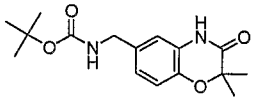
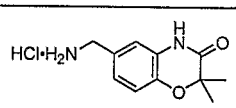
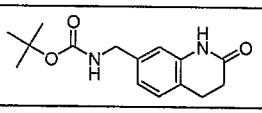
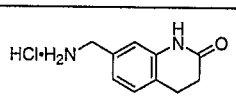
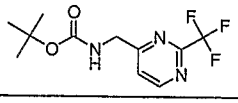
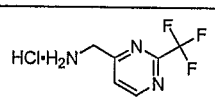
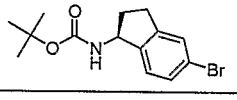
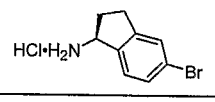
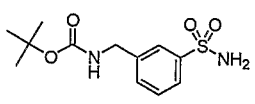
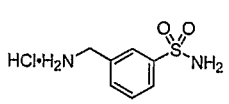
[0357] Step A

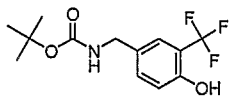
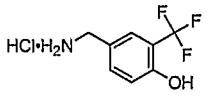
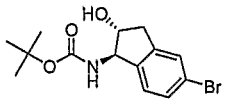
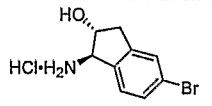
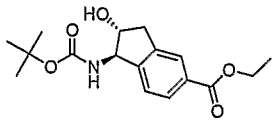
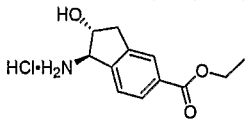
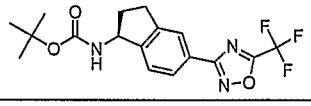
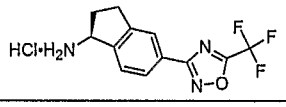
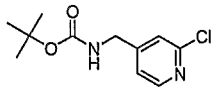
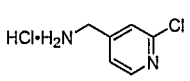
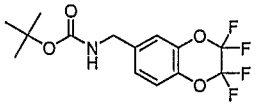
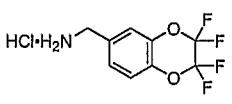
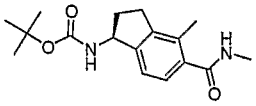
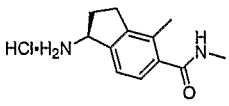
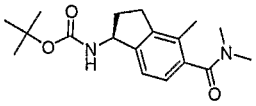
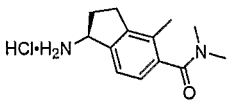
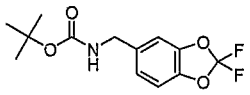
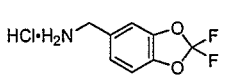
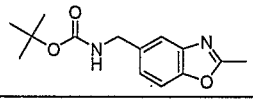
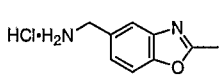
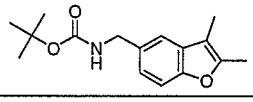
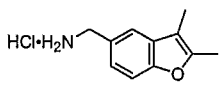
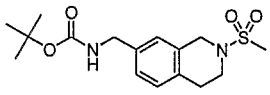
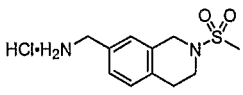
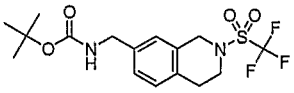
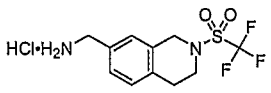
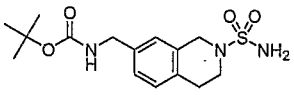
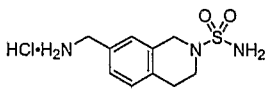
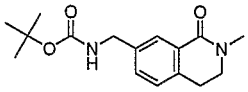
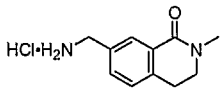
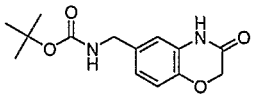
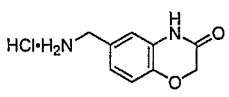
To a suspension of the title compound from the Preparative Example 110, Step B (52 mg) in EtOAc (600 μL) was added a 4M solution of HCl in 1,4-dioxane (600 μL). The reaction mixture was stirred at room temperature for 1½ h and concentrated to afford the title compound (43 mg, 99%). $[M\text{-}Cl]^+ = 250$.

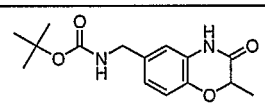
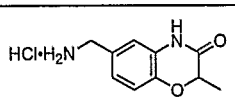
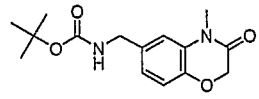
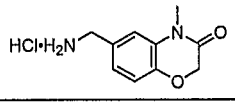
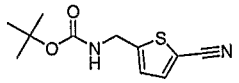
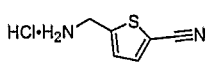
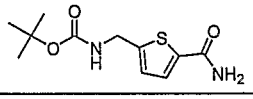
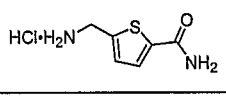
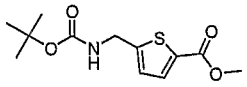
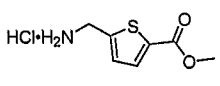
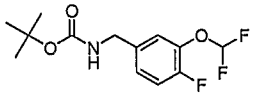
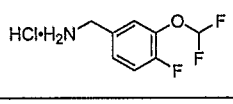
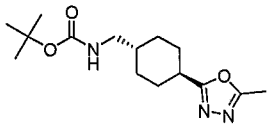
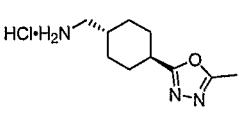
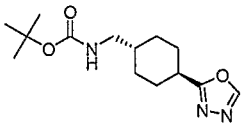
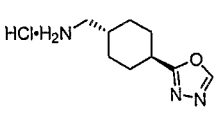
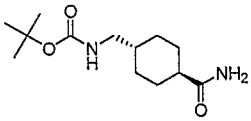
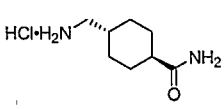
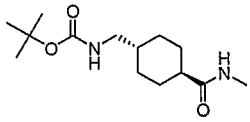
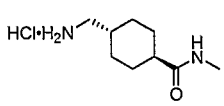
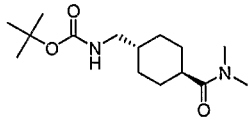
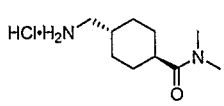
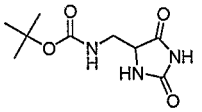
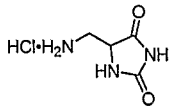
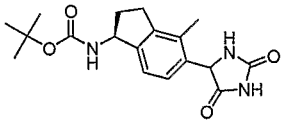
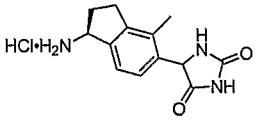
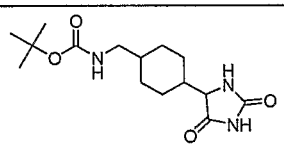
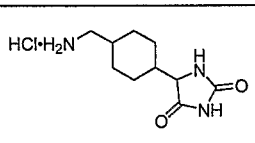
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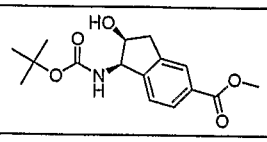
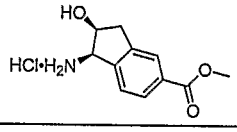
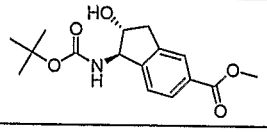
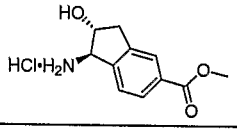
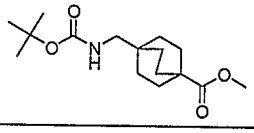
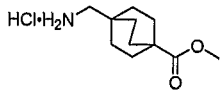
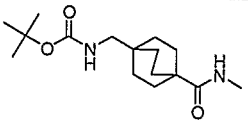
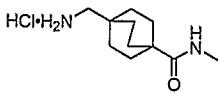
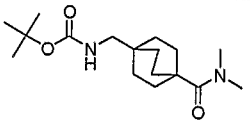
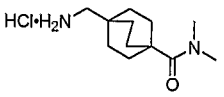
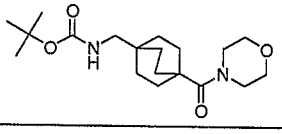
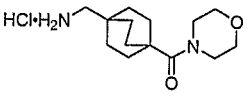
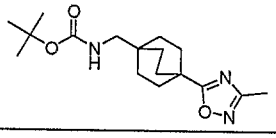
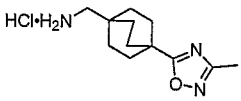
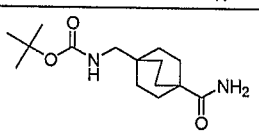
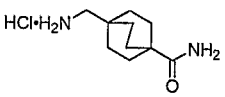
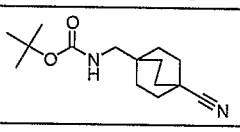
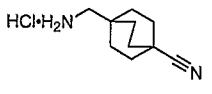
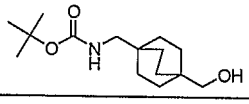
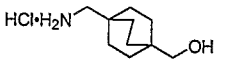
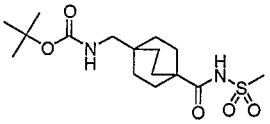
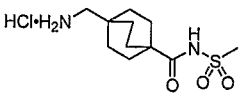
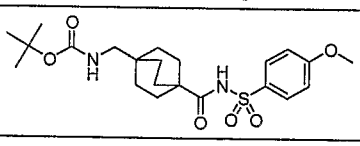
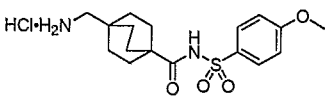
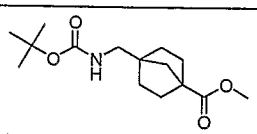
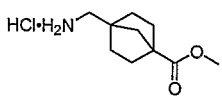
[0358] Following a similar procedure as described in the Preparative Example 133, except using the protected amines indicated in Table I-7 below, the following compounds were prepared.

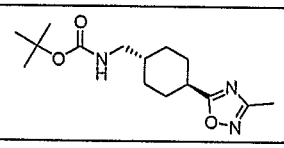
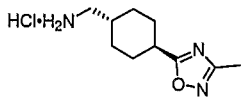
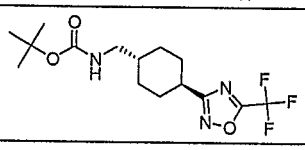
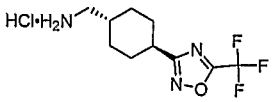
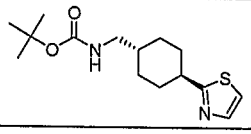
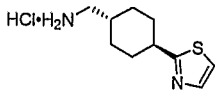
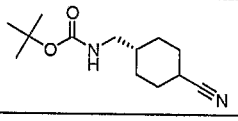
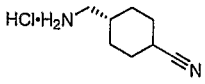
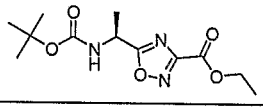
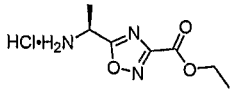
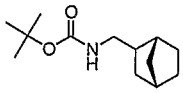
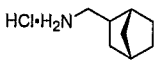
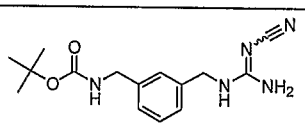
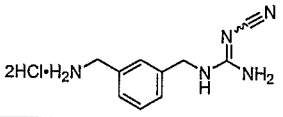
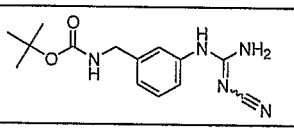
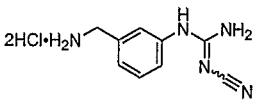
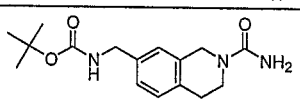
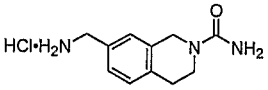
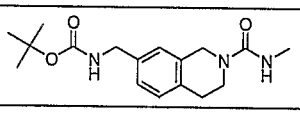
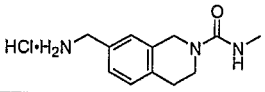
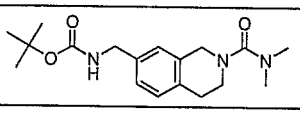
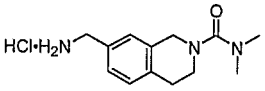
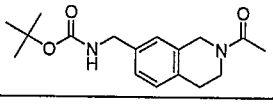
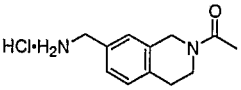
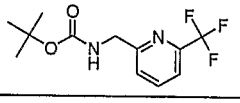
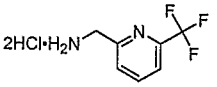
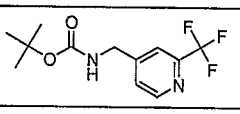
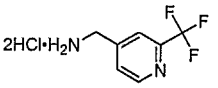
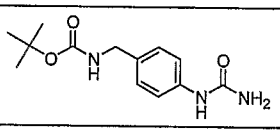
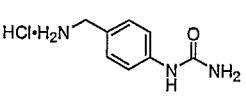
Table I-7

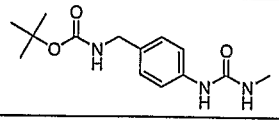
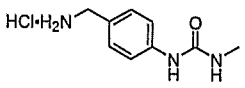
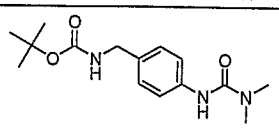
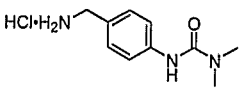
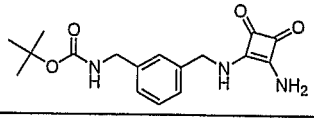
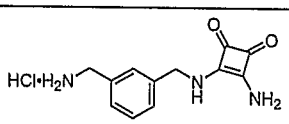
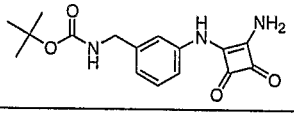
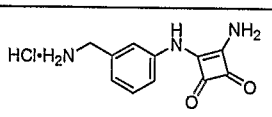
Prep. Ex. #	protected amine	product	yield
134			>99% $[M\text{-}NH_3Cl]^+ = 156$
135			>99% $[M\text{-}Cl]^+ = 159$
136			99% $[M\text{-}Cl]^+ = 218$
137			>99% $[M\text{-}Cl]^+ = 232$
138			>99% $[M\text{-}NH_3Cl]^+ = 215$
139			>99% $[M\text{-}NH_3Cl]^+ = 201$
140			>99% $[M\text{-}Cl]^+ = 198$
141			99% $[M\text{-}Cl]^+ = 207$
142			64% $[M\text{-}Cl]^+ = 177$
143			>99% $[M\text{-}Cl]^+ = 178$
144			>99% $[M\text{-}NH_3Cl]^+ = 195/197$
145			67% (over 2 steps) $[M\text{-}Cl]^+ = 187$

Prep. Ex. #	protected amine	product	yield
146			>99% $[M-Cl]^+ = 192$
147			n.d. $[M-NH_3Cl]^+ = 210/212$
148			81% $[M-Cl]^+ = 222$
149			77% $[M-NH_3Cl]^+ = 253$
150			>99% $[M-Cl]^+ = 143$
151			>99% $[M-Cl]^+ = 238$
152			>99% $[M-Cl]^+ = 191$
153			>99% $[M-Cl]^+ = 205$
154			>99% $[M-NH_3Cl]^+ = 188$
155			>99% $[M-Cl]^+ = 163$
156			>99% $[M-NH_3Cl]^+ = 159$
157			>99% $[M-Cl]^+ = 241$
158			>99% $[M-Cl]^+ = 295$
159			>99% $[M-Cl]^+ = 242$
160			>99% $[M-Cl]^+ = 191$
161			>99% $[M-NH_3Cl]^+ = 162$

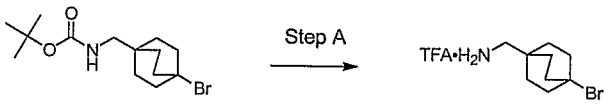
Prep. Ex. #	protected amine	product	yield
162			>99% $[M\text{-}NH_3Cl]^+ = 176$
163			>99% $[M\text{-}Cl]^+ = 193$
164			96% $[M\text{-}Cl]^+ = 139$
165			>99% $[M\text{-}Cl]^+ = 157$
166			>99% $[M\text{-}NH_3Cl]^+ = 155$
167			>99% $[M\text{-}Cl]^+ = 192$
168			95% $[M\text{-}Cl]^+ = 196$
169			>99% $[M\text{-}Cl]^+ = 182$
170			99% $[M\text{-}Cl]^+ = 157$
171			99% $[M\text{-}Cl]^+ = 171$
172			98% $[M\text{-}Cl]^+ = 185$
173			93% $[M\text{-}Cl]^+ = 130$
174			>99% $[M\text{-}Cl]^+ = 246$
175			>99% $[M\text{-}Cl]^+ = 212$

Prep. Ex. #	protected amine	product	yield
176			>99% $[M-NH_3Cl]^+ = 191$
177			>99% $[M-NH_3Cl]^+ = 191$
178			>99% $[M-Cl]^+ = 198$
179			>99% $[M-Cl]^+ = 197$
180			>99% $[M-Cl]^+ = 211$
181			>99% $[M-Cl]^+ = 253$
182			>99% $[M-Cl]^+ = 223$
183			>99% $[M-Cl]^+ = 183$
184			>99% $[M-Cl]^+ = 165$
185			>99% $[M-Cl]^+ = 170$
186			>99% $[M-Cl]^+ = 261$
187			>99% $[M-Cl]^+ = 353$
188			>99% $[M-Cl]^+ = 184$

Prep. Ex. #	protected amine	product	yield
189			n.d. $[M\text{-}Cl]^+ = 196$
190			n.d. $[M\text{-}Cl]^+ = 250$
191			n.d. $[M\text{-}Cl]^+ = 197$
192			n.d. $[M\text{-}Cl]^+ = 139$
193			n.d. $[M\text{-}Cl]^+ = 286$
194			n.d. $[M\text{-}Cl]^+ = 286$
195			>99% $[M\text{-}HCl_2]^+ = 204$
196			94% $[M\text{-}HCl_2]^+ = 190$
197			99% $[M\text{-}Cl]^+ = 206$
198			99% $[M\text{-}Cl]^+ = 220$
199			99% $[M\text{-}Cl]^+ = 134$
200			99% $[M\text{-}Cl]^+ = 205$
201			92% $[M\text{-}HCl_2]^+ = 177$
202			>99% $[M\text{-}HCl_2]^+ = 177$
203			99% $[M\text{-}Cl]^+ = 166$

Prep. Ex. #	protected amine	product	yield
204			99% $[M-Cl]^+ = 180$
205			99% $[M-Cl]^+ = 194$
206			98% $[M-Cl]^+ = 232$
207			>99% $[M-NH_3Cl]^+ = 218$

Preparative Example 208



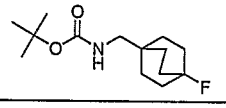
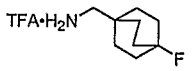
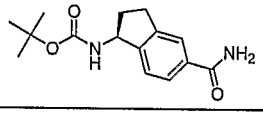
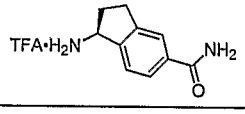
[0359] Step A

To a ice cooled solution of the title compound from the Preparative Example 73 (89 mg) in $CHCl_3$ (3 mL) was added a solution of trifluoroacetic acid (1.5 mL) in $CHCl_3$ (1.5 mL). The mixture was stirred at 0°C for 5 min, then the cooling bath was removed and the mixture was stirred at room temperature for 1½ h. The mixture was concentrated, dissolved in CH_3CN (5 mL), again concentrated and dried in vacuo to afford the title compound (93 mg, >99%). $[M-TFA]^+ = 218/220$.

Preparative Examples 209-210

[0360] Following a similar procedure as described in the Preparative Example 208, except using the protected amines indicated in Table I-8 below, the following compounds were prepared.

Table I-8

Prep. Ex. #	protected amine	product	yield
209			>99% $[M\text{-}TFA]^+ = 158$
210			93% $[M\text{-}(NH_2\bullet TFA)]^+ = 160$

Preparative Example 211



[0361] Step A

Commercially available 3-aminomethyl-benzoic acid methyl ester hydrochloride (500 mg) was dissolved in a 33% solution of NH_3 in H_2O (50 mL) and heated in a sealed pressure tube to 90°C for 20 h. Cooling to room temperature and concentration afforded the title compound (469 mg, >99%). $[M\text{-}Cl]^+ = 151$..

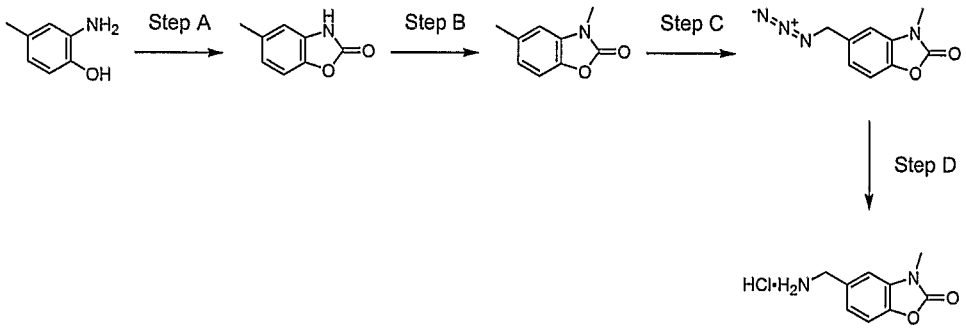
Preparative Example 212



[0362] Step A

Commercially available 3-aminomethyl-benzoic acid methyl ester hydrochloride (100 mg) was dissolved in a 40% solution of $MeNH_2$ in H_2O (20 mL) and heated in a sealed pressure tube to 90°C for 20 h. Cooling to room temperature and concentration afforded the title compound (107 mg, >99%). $[M\text{-}Cl]^+ = 165$.

Preparative Example 213



[0363] Step A

A mixture of commercially available 2-hydroxy-5-methylaniline (5.2 g) and *N,N'*-carbonyldiimidazole (6.85 g) in dry THF (60 mL) was heated to reflux for 6 h, cooled to room temperature, poured on ice and adjusted to pH 4 with 6N aqueous HCl. The formed precipitate was isolated by filtration, dried and recrystallized from toluene to afford the title compound as a grey solid (4.09 g, 65%).

[0364] Step B

The title compound from Step A above (1.5 g), K_2CO_3 (1.7 g) and methyl iodide (6 mL) were dissolved in dry DMF (15 mL). The mixture was stirred at 50°C for 2 h, concentrated and acidified to pH 4 with 1N HCl. The precipitate was isolated by filtration and dried to afford the title compound as an off-white solid (1.48 g, 90%). ^{1}H-NMR ($CDCl_3$) □= 7.05 (s, 1 H), 6.90 (d, 1 H), 6.77 (s, 1 H), 3.38 (s, 3 H), 2.40 (s, 3 H).

[0365] Step C

The title compound from Step B above (1.1 g), *N*-bromosuccinimide (1.45 g) and α,α'-azoisobutyronitrile (150 mg) were suspended in CCl_4 (50 mL), degassed with argon and heated to reflux for 1 h. The mixture was cooled, filtered, concentrated and dissolved in dry DMF (20 mL). Then NaN_3 (1 g) was added and the mixture was vigorously stirred for 3 h, diluted with EtOAc, washed subsequently with H_2O and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound as colorless needles (963 mg, 70%). ^{1}H-NMR ($CDCl_3$) □= 7.07 (s, 1 H), 6.98 (d, 1 H), 6.88 (s, 1 H), 4.25 (s, 2 H), 3.36 (s, 3 H).

[0366] Step D

A mixture of he title compound from Step C above (963 mg) and PPh_3 (1.36 g) in THF (30 mL) were stirred for 14 h, then H_2O was added and stirring was continued for 2 h. The mixture was concentrated and coevaporated twice with toluene. The remaining residue was diluted with dry dioxane and a 4M solution of HCl in 1,4-dioxane (1.5 mL) was added. The formed precipitate was isolated by filtration and dried to afford the title compound as a colorless solid (529 mg, 52%). $[M–Cl]^+ = 179$.

Preparative Example 214



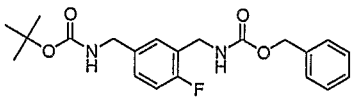
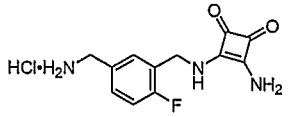
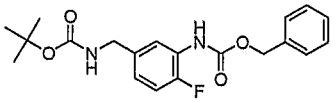
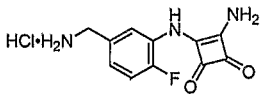
[0367] Step A

A mixture of the title compound from the Preparative Example 95, Step A (1.81 g) and Pd/C (10wt%, 200 mg) in EtOH (50 mL) was hydrogenated at atmospheric pressure overnight, filtered and concentrated to a volume of ~20 mL. 3,4-Diethoxy-3-cyclobutene-1,2-dione (0.68 mL) and NEt_3 (0.5 mL) were added and the mixture was heated to reflux for 4 h. Concentration and purification by chromatography (silica, cyclohexane/EtOAc) afforded a slowly crystallizing colorless oil. This oil was dissolved in EtOH (20 mL) and a 28% solution of NH_3 in H_2O (100 mL) was added. The mixture was stirred for 3 h, concentrated, slurried in H_2O, filtered and dried under reduced pressure. The remaining residue was dissolved in a 4M solution of HCl in 1,4-dioxane (20 mL), stirred for 14 h, concentrated, suspended in Et_2O, filtered and dried to afford the title compound as an off-white solid (1.08 g, 92%). $[M-Cl]^+ = 258$.

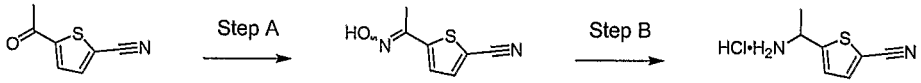
Preparative Examples 215-216

[0368] Following a similar procedure as described in the Preparative Example 214, except using the intermediates indicated in Table I-9 below, the following compounds were prepared.

Table I-9

Ex. #	intermediate	product	yield
215			n.d. $[M\text{-}Cl]^+ = 250$
216			67% $[M\text{-}NH_3Cl]^+ = 236$

Preparative Example 217



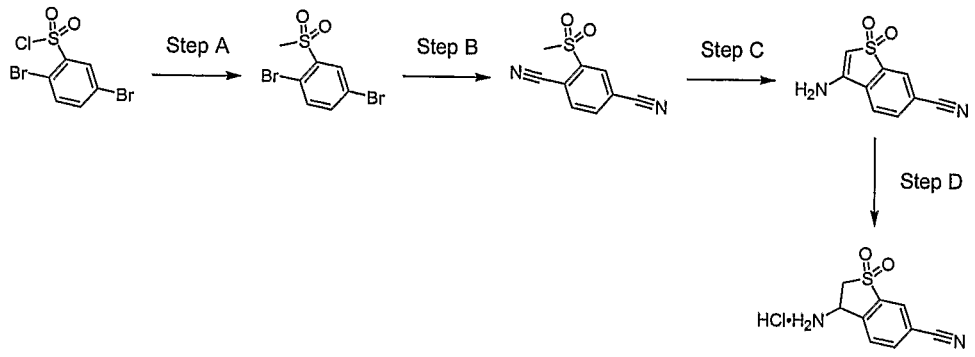
[0369] Step A

Commercially available 5-acetyl-thiophene-2-carbonitrile (2.5 g) was stirred with hydroxylamine hydrochloride (0.6 g) and NaOAc (0.6 g) in dry MeOH (30 mL) for 1½ h. The mixture was concentrated, diluted with EtOAc, washed subsequently with H_2O and saturated aqueous NaCl dried ($MgSO_4$), filtered and absorbed on silica. Purification by chromatography (silica, cyclohexane/EtOAc) afforded the title compound as a colorless solid (844 mg, 31%). $[MH]^+ = 167$.

[0370] Step B

To a solution of the title compound from Step A above (844 mg) in AcOH (30 mL) was added zinc dust (1.7 g). The mixture was stirred for 5 h, filtered, concentrated, diluted with $CHCl_3$, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and filtered. Treatment with a 4M solution of HCl in 1,4-dioxane (2 mL) and concentration afforded the title compound as an off-white solid (617 mg, 64%). $[M\text{-}NH_3Cl]^+ = 136$.

Preparative Example 218



[0371] Step A

A suspension of commercially available 2,5-dibromobenzenesulfonyl chloride (1.0 g), Na_2SO_3 (0.46 g) and NaOH (0.27 g) in H_2O (10 mL) was heated to 70°C for 5 h. To the cooled solution was added methyl iodide (4 mL) and MeOH. The biphasic system was stirred vigorously at 50°C overnight, concentrated and suspended in H_2O. Filtration afforded the title compound as colorless needles (933 mg, 99%). $[MH]^+ = 313/315/317$.

[0372] Step B

Under an argon atmosphere in a sealed tube was heated a mixture of the title compound from Step A above (8.36 g) and CuCN (7.7 g) in degassed *N*-methylpyrrolidone (30 mL) to 160°C overnight. Concentration, absorbtion on silica and purification by chromatography (silica, cyclohexane/EtOAc) afforded the title compound as beige crystals (1.08 g, 20%).

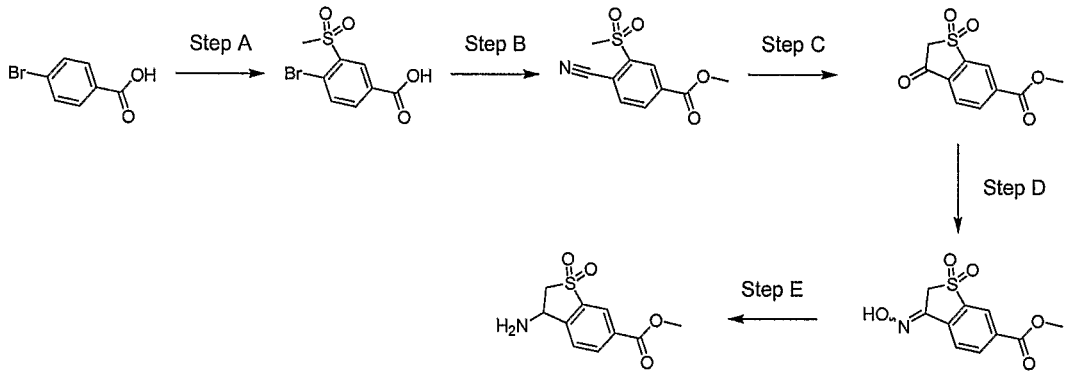
[0373] Step C

A mixture of the title compound from Step B above (980 mg) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (0.72 mL) in degassed DMSO was heated to 50°C for 45 min under an argon atmosphere. The solution was diluted with EtOAc, washed subsequently with 10% aqueous citric acid and saturated aqueous NaCl, dried ($MgSO_4$), concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound as a bright yellow solid (694 mg, 71%). ^{1}H-NMR (CD_3CN) □= 8.00-8.10 (m, 2 H), 7.72 (d, 1 H), 5.75 (br s, 2 H), 5.70 (s, 1 H).

[0374] Step D

A mixture of the title compound from Step C above (892 mg) and Pd/C (10wt%, 140 mg) in DMF (10 mL) was hydrogenated at atmospheric pressure for 2 h and then filtered. Di-*tert*-butyl dicarbonate (440 mg) was added and the mixture was stirred overnight. The mixture was concentrated, diluted with EtOAc, washed subsequently with 10% aqueous citric acid and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated. Purification by chromatography (silica, cyclohexane/EtOAc) afforded a colorless solid, which was stirred in a 4M solution of HCl in 1,4-dioxane (20 mL) overnight and then concentrated to give the title compound as colorless crystals (69 mg, 8%). $[M–Cl]^+ = 209$.

Preparative Example 219



[0375] Step A

A solution of commercially available 4-bromobenzoic acid (24 g) in chlorosulfonic acid (50 mL) was stirred at room temperature for 2 h and then heated to 150°C for 3 h. The mixture was cooled to room temperature and poured on ice (600 mL). The formed precipitate was collected by filtration and washed with H_2O. To the obtained solid material were added H_2O (300 mL), Na_2SO_3 (20 g) and NaOH (17 g) and the resulting mixture was stirred at 80°C for 5 h. Then the mixture was cooled to room temperature and diluted with MeOH (250 mL). Iodomethane (100 mL) was slowly added and the mixture was heated to reflux overnight. Concentration, acidification, cooling and filtration afforded the title compound as a white powder (28.0 g, 84%). $[MH]^+ = 279/281$.

[0376] Step B

To a solution of the title compound from Step A above (5.0 g) in dry MeOH (120 mL) was slowly added $SOCl_2$ (4 mL). The resulting mixture was heated to reflux for 4 h, concentrated and diluted with NMP (20 mL). CuCN (1.78 g) was added and the resulting mixture was heated in a sealed tube under an argon atmosphere to 160°C overnight. The mixture was concentrated, absorbed on silica and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound as colorless needles (976 mg, 23%). $[MH]^+ = 240$.

[0377] Step C

To a solution of the title compound from Step B above (1.89 g) in MeOH (40 mL) and was added NaOMe (1.3 g). The mixture was heated to reflux for 90 min, cooled to room temperature, diluted with concentrated HCl (2 mL) and H_2O (10 mL) and heated again to reflux for 30 min. The mixture was concentrated, diluted with EtOAc, washed with saturated aqueous NaCl, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound as colorless crystals (682 mg, 36%). $[MH]^+ = 241$.

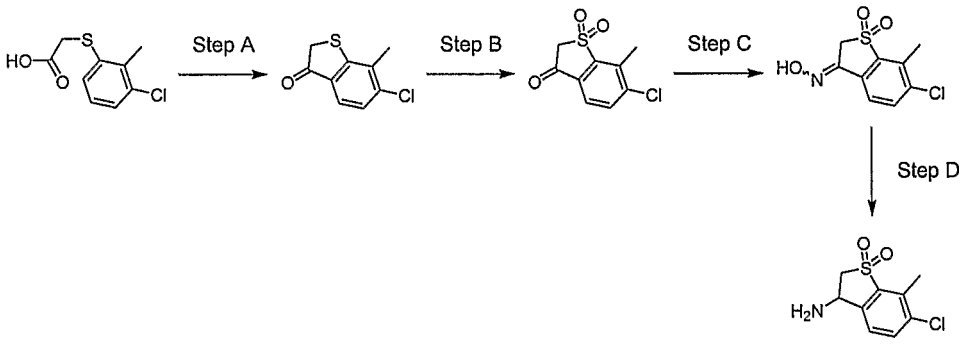
[0378] Step D

A solution the title compound from Step C above (286 mg), NaOAc (490 mg) and hydroxylamine hydrochloride (490 mg) in dry MeOH (20 mL) was heated to reflux for 2½ h. The mixture was concentrated, dissolved in EtOAc, washed with saturated aqueous NaCl and concentrated to afford the title compound as an off-white solid (302 mg, 99%). ^{1}H-NMR (DMSO): □= 12.62 (s, 1 H), 8.25-8.28 (m, 2 H), 8.04 (d, 1 H), 4.57 (s, 2 H), 3.90 (s, 3 H).

[0379] Step E

The title compound from Step D above (170 mg) was dissolved in MeOH (50 mL) and heated to 60°C. Then zinc dust (500 mg) and 6N aqueous HCl (5 mL) were added in portions over a period of 30 min. The mixture was cooled, filtered, concentrated, diluted with EtOAc, washed subsequently with a saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated to afford the title compound as a yellow oil (128 mg, 80%). $[MH]^+ = 242$.

Preparative Example 220



[0380] Step A

To a solution of commercially available 2-[(3-chloro-2-methylphenyl)thio]acetic acid (2.1 g) in DMF (3 drops) was added dropwise oxalyl chloride (5 mL). After 1.5 h the mixture was concentrated, redissolved in 1,2-dichloroethane (20 mL) and cooled to –10°C. $AlCl_3$ (1.6 g) was added and the cooling bath was removed. The mixture was stirred for 1 h, poured on ice and extracted with CH_2Cl_2 to afford the crude title compound as a brown solid (2.01 g). $[MH]^+ = 199$.

[0381] Step B

To a solution of the title compound from Step A above (1.01 g) in CH_2Cl_2 (40 mL) was added mCPBA (70-75%, 1.14 g) at room temperature. The mixture was stirred for 1 h, diluted with CH_2Cl_2, washed subsequently with 1N aqueous HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated. Purification by chromatography (silica, cyclohexane/EtOAc) afforded the title compound as a colorless solid (668 mg). $[MH]^+ = 231$.

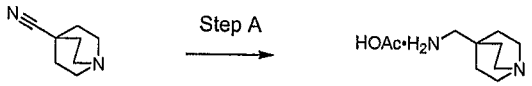
[0382] Step C

A mixture of the title compound from Step B above (430 mg), NaOAc (800 mg) and hydroxylamine hydrochloride (800 mg) in dry MeOH (20 mL) was heated to reflux for 2 h. The mixture was concentrated, dissolved in EtOAc, washed with saturated aqueous NaCl and concentrated to afford the title compound as colorless crystals (426 mg, 93%). $[MH]^+ = 246$.

[0383] Step D

The title compound from Step C above (426 mg) was dissolved in MeOH (50 mL) and heated to 60°C. Then zinc dust (1.3 g) and 6N aqueous HCl (20 mL) were added in portions over a period of 30 min. The mixture was cooled, filtered, concentrated, diluted with $CHCl_3$, washed subsequently with a saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated to afford the title compound as an off-white solid (313 mg, 78%). $[MH]^+ = 232$.

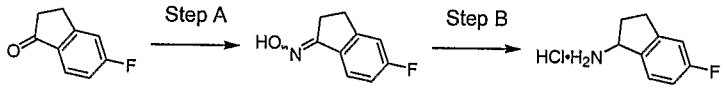
Preparative Example 221



[0384] Step A

A mixture of commercially available 1-aza-bicyclo[2.2.2]octane-4-carbonitrile (0.5 g), AcOH (1 mL) and Pd/C (10wt%, 200 mg) in THF (20 mL) was hydrogenated at atmospheric pressure overnight, filtered and concentrated to afford the crude title compound as a brown solid. $[M\text{-}OAc]^+ = 141$.

Preparative Example 222



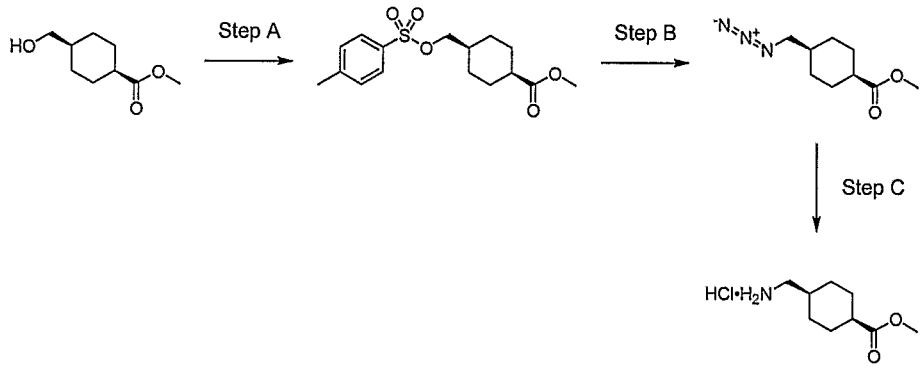
[0385] Step A

Commercially available 5-fluoroindanone (1.0 g) was treated similarly as described in the Preparative Example 220, Step C to afford the title compound as a colorless solid (1.3 g, >99%). $[MH]^+ = 166$.

[0386] Step B

The title compound from Step A above (1.35 g) was treated similarly as described in the Preparative Example 217, Step B to afford the title compound as a colorless solid (36.5 mg). $[M\text{-}NH_3Cl]^+ = 135$.

Preparative Example 223



[0387] Step A

To an ice cooled solution of commercially available *cis*-4-hydroxymethyl-cyclohexanecarboxylic acid methyl ester (330 mg) in CH_2Cl_2/pyridine (3:1, 4 mL) was added 4-toluenesulfonic acid chloride (0.49 g). The mixture was stirred at room temperature overnight, cooled to 0°C, quenched with 2N aqueous HCl (35 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated to afford the title compound (643 mg, >99%). $[MH]^+ = 327$.

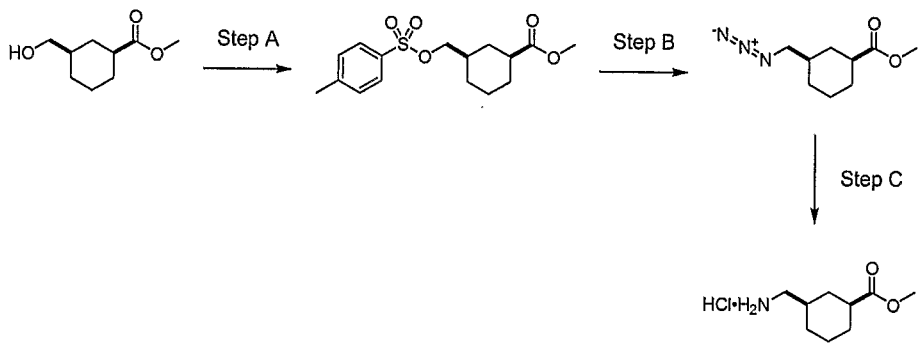
[0388] Step B

A mixture of the title compound from Step A above (643 mg) and NaN_3 (636 mg) in DMA (5 mL) was stirred at 70°C overnight. The mixture was concentrated and diluted with EtOAc (25 mL), H_2O (5 mL) and saturated aqueous NaCl (5 mL). The organic phase was separated, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound (299 mg, 77%). $[MNa]^+ = 220$.

[0389] Step C

A mixture of the title compound from Step B above (299 mg) and Pd/C (10wt%, 50 mg) in MeOH (10 mL) was hydrogenated at atmospheric pressure for 4 h, filtered and concentrated. The remaining residue was taken up in MeOH (7 mL), treated with 1N HCl in Et_2O (6 mL) and concentrated to afford the crude title compound (248 mg, 95%). $[MH]^+ = 172$.

Preparative Example 224



[0390] Step A

Commercially available *cis*-3-hydroxymethyl-cyclohexanecarboxylic acid methyl ester (330 mg) was treated similarly as described in the Preparative Example 223, Step A to afford the title compound (606 mg, 97%). $[MH]^+ = 327$.

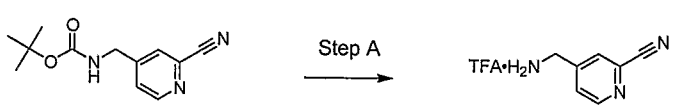
[0391] Step B

The title compound from Step A above (606 mg) was treated similarly as described in the Preparative Example 223, Step B to afford the title compound (318 mg, 87%). $[MNa]^+ = 220$.

[0392] Step C

The title compound from Step B above (318 mg) was treated similarly as described in the Preparative Example 223, Step C to afford the crude title compound (345 mg, >99%). $[MH]^+ = 172$.

Preparative Example 225



[0393] Step A

To a suspension of commercially available (3-cyano-benzyl)-carbamic acid *tert*-butyl ester (50 mg) in $CHCl_3$ (2 mL) were successively added triethylsilane (0.5 mL) and trifluoroacetic acid (5 mL). The mixture was stirred at room temperature for 2 h and then concentrated to afford the crude title compound. $[M\text{-}TFA]^+ = 134$.

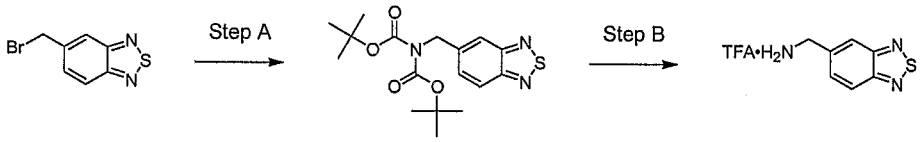
Preparative Example 226



[0394] Step A

To a stirred solution of KOH (1.2 g) in EtOH (10 mL) was added commercially available bis(*tert*-butyldicarbonyl) amine (4.5 g). The mixture was stirred at room temperature for 1 h and then diluted with Et_2O. The formed precipitate was collected by filtration and washed with Et_2O (3 x 10 mL) to afford the title compound (3.4 g, 64%).

Preparative Example 227



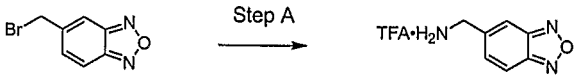
[0395] Step A

To a stirred solution of the title compound from the Preparative Example 226, Step A (160 mg) in DMF (2 mL) was added a solution of commercially available 5-bromomethyl-benzo[1,2,5]thiadiazole (115 mg) in DMF (1 mL). The mixture was stirred at 50°C for 2 h, concentrated, diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated to afford the crude title compound (180 mg, 71%). $[MH]^+ = 366$.

[0396] Step B

A solution of the title compound from Step A above (180 mg) in trifluoroacetic acid (2 mL) was stirred at room temperature for 1 h at room temperature and then concentrated to afford the title compound (140 mg, >99%). $[M\text{-}TFA]^+ = 166$.

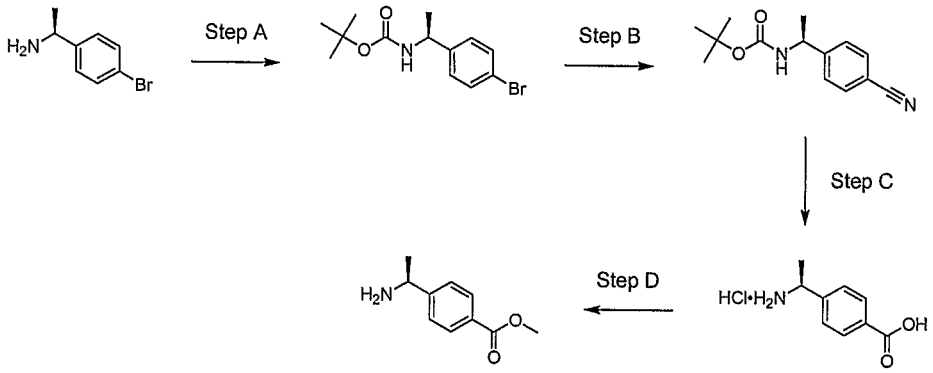
Preparative Example 228



[0397] Step A

Commercially available 5-bromomethyl-benzo[1,2,5]oxadiazole was treated similarly as described in the Preparative Example 227 to afford the title compound. $[M\text{-}TFA]^+ = 150$.

Preparative Example 229



[0398] Step A

Commercially available (*S*)-(–)-1-(4-bromophenyl)ethylamine (2.0 g) was treated similarly as described in the Preparative Example 3, Step D to afford the title compound as a white solid (2.5 g, 92%). ^{1}H-NMR ($CDCl_3$) □= 7.43 (d, 2 H), 7.17 (d, 2 H), 4.72 (br s, 2 H), 1.35 (br s, 12 H).

[0399] Step B

The title compound from Step A above (4.0 g) was treated similarly as described in the Preparative Example 3, Step E to afford the title compound (2.0 g, 60%). $[MH]^+ = 247$.

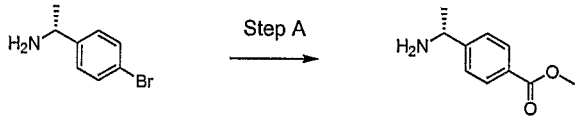
[0400] Step C

The title compound from Step B above (2.0 g) was treated similarly as described in the Preparative Example 2, Step A to afford the title compound (1.8 g, >99%). $[M\text{-}Cl]^+ = 166$.

[0401] Step D

The title compound from Step C above (1.0 g) was treated similarly as described in the Preparative Example 2, Step B to afford the title compound (310 mg, 35%). $[MH]^+ = 180$.

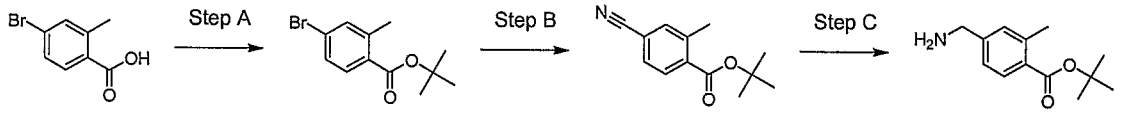
Preparative Example 230



[0402] Step A

If one were to follow a similar procedure as described in the Preparative Example 229, except using commercially available (*R*)-(+)-1-(4-bromophenyl)ethylamine instead of (*S*)-(–)-1-(4-bromophenyl)ethylamine, one would obtain the title compound.

Preparative Example 231



[0403] Step A

To a solution of commercially available 4-bromo-2-methyl-benzoic acid (1.5 g) in anhydrous CH_2Cl_2 (10 mL) was added *tert*-butyl 2,2,2-trichloroacetimidate (3.0 mL). The resulting mixture was heated to reflux for 24 h, cooled to room temperature, concentrated and purified by chromatography (silica, CH_2Cl_2) to give the desired title compound (1.0 g, 52%). $[MH]^+ = 271$.

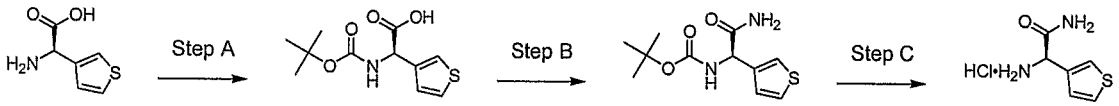
[0404] Step B

A mixture of the title compound from Step A above (1.0 g), $Zn(CN)_2$ (1.0 g) and $Pd(PPh_3)_4$ (1.0 g) in anhydrous DMF (15 mL) was heated at 110°C under a nitrogen atmosphere for 18 h, concentrated and purified by chromatography (silica, hexane/CH_2Cl_2) to give the desired title compound (0.6 g, 75%). $[MH]^+ = 218$.

[0405] Step C

To a solution of the title compound from Step B above (0.55 g), in anhydrous CH_2Cl_2 (30 mL) was added Bu_4NBH_4 (1.30 g). The mixture was heated to reflux under a nitrogen atmosphere for 12 h and then cooled to room temperature. 1N aqueous NaOH (5 mL) was added and the mixture was stirred for 20 min before it was concentrated. The remaining residue was then taken up in Et_2O (150 mL), washed with 1N aqueous NaOH (25 mL) and saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated to give the title compound (0.50 g, 89%). $[MH]^+ = 222$.

Preparative Example 232



[0406] Step A

A solution of commercially available (*R*)-amino-thiophen-3-yl-acetic acid (0.50 g), 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (0.86 g) and NEt_3 (0.65 mL) in 1,4-dioxane/H_2O (3:2, 7 mL) was stirred for 24 h, concentrated to $^1/_3$ volume and diluted with H_2O (100 mL). The resulting aqueous mixture was extracted with Et_2O (100 mL), acidified with 1N aqueous HCl and extracted with Et_2O (2 x 80 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give the desired title compound (0.7 g, 86%). $[MH]^+ = 258$.

[0407] Step B

To a stirred mixture of the title compound from Step A above (0.43 g) and $(NH_4)_2CO_3$ (0.48 g) in 1,4-dioxane/DMF (6:1, 3.5 mL) were added pyridine (0.4 mL) and di-*tert*-butyl dicarbonate (0.50 g). The mixture was stirred for 48 h, diluted with EtOAc (40 mL), washed with 1N aqueous HCl and saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated to give the desired title compound, which was not further purified (0.35 g, 86%). $[MH]^+ = 257$.

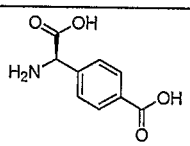
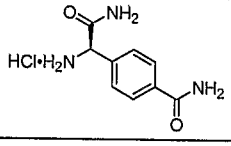
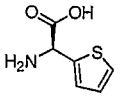
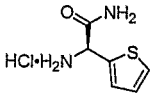
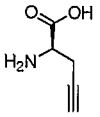
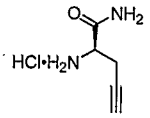
[0408] Step C

The title compound from Step B above (0.35 g) was taken up in a 4M solution of HCl in 1,4-dioxane (10 mL). The mixture was stirred overnight and concentrated to give the title compound (0.15 g, n.d.). $[MH]^+ = 157$.

Preparative Examples 233-235

[0409] Following a similar procedure as described in the Preparative Example 232, except using the amino acids indicated in Table I-10 below, the following compounds were prepared.

Table I-10

Prep. Ex. #	amino acid	product	yield
233			n.d. $[M-Cl]^+ = 194$
234			n.d. $[M-Cl]^+ = 157$
235			n.d. $[M-Cl]^+ = 113$

Preparative Example 236



[0410] Step A

Commercially available (*R*)-2-amino-4,4-dimethyl-pentanoic acid (250 mg) was treated similarly as described in the Preparative Example 232, Step A to afford the title compound (370 mg, 87%). $[MNa]^+ = 268$.

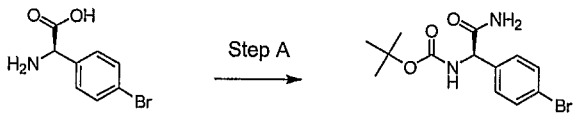
[0411] Step B

The title compound from Step A above (370 mg) was treated similarly as described in the Preparative Example 232, Step B to afford the title compound. $[MNa]^+ = 267$.

[0412] Step C

The title compound from Step B above was treated similarly as described in the Preparative Example 208, Step A to afford the title compound (30 mg, 14% over 2 steps). $[M\text{-}TFA]^+ = 145$.

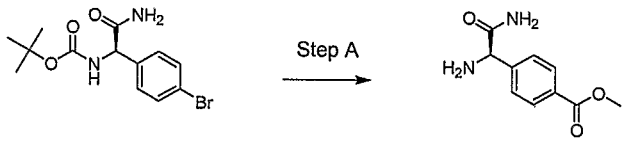
Preparative Example 237



[0413] Step A

If one were to follow a similar procedure as described in the Preparative Example 232, Step A and Step B, except using commercially available (*R*)-amino-(4-bromo-phenyl)-acetic acid instead of (*R*)-amino-thiophen-3-yl-acetic acid in Step A, one would obtain the title compound.

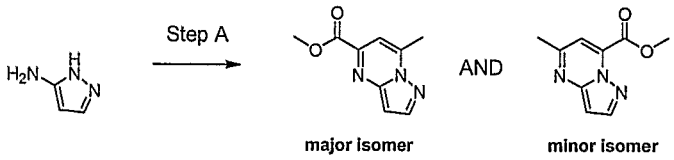
Preparative Example 238



[0414] Step A

If one were to follow a similar procedure as described in the Preparative Example 229, Step B to Step D, except using the title compound from the Preparative Example 237, Step A instead of (*R*)-amino-thiophen-3-yl-acetic acid, one would obtain the title compound.

Preparative Example 239

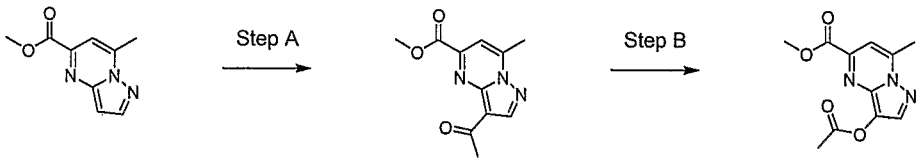


[0415] Step A

To a solution of commercially available 1*H*-pyrazol-5-amine (86.4 g) in MeOH (1.80 L) was added commercially available methyl acetopyruvate (50.0 g). The mixture was heated to reflux for 5 h and then cooled to room temperature overnight. The precipitated yellow needles were collected by filtration and the supernatant was concentrated at 40°C under reduced pressure to ~$^2/_3$ volume until more precipitate began to form. The mixture was cooled to room temperature and the precipitate was collected by filtration. This concentration/ precipitation/filtration procedure was repeated to give 3 batches. This material was combined and recrystallized from MeOH to give the major isomer of the title compound (81.7 g, 72%). $[MH]^+ = 192$.

[0416] The remaining supernatants were combined, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the minor isomer of title compound (6.8 g, 6%). $[MH]^+ = 192$.

Preparative Example 240



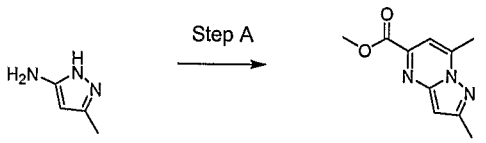
[0417] Step A

To a solution of the major isomer of the title compound from the Preparative Example 239, Step A (2.0 g) in CH_2Cl_2 (20 mL) were added acetyl chloride (3.0 mL) and $SnCl_4$ (10.9 g). The resulting mixture was heated to reflux overnight, cooled and quenched with H_2O (10 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x). The combined organic phases were concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound (1.2 g, 49%). $[MH]^+ = 234$.

[0418] Step B

Trifluoroacetic anhydride (4.6 mL) was added dropwise to an ice cooled suspension of urea hydrogen peroxide (5.8 g) in CH_2Cl_2 (40 mL). The mixture was stirred for 30 min, then a solution of the title compound from Step A above (1.8 g) in CH_2Cl_2 (20 mL) was added and the mixture was stirred at room temperature overnight. $NaHSO_3$ (1.0 g) was added and the resulting mixture was diluted with saturated aqueous $NaHCO_3$ (40 mL). The aqueous phase was separated and extracted with CH_2Cl_2. The combined organic phases were concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound (500 mg, 26%). ^{1}H-NMR ($CDCl_3$) □= 8.40 (s, 1 H), 7.47 (d, 1 H), 4.03 (s, 3 H), 2.84 (d, 3 H), 2.42 (s, 3 H).

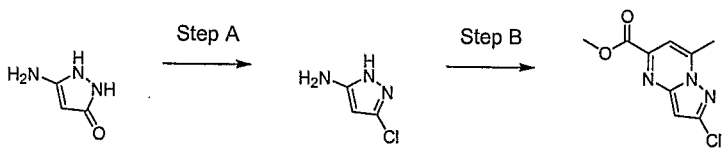
Preparative Example 241



[0419] Step A

A mixture of commercially available 5-amino-3-methylpyrazole (1.44 g) and methyl acetopyruvate (0.97 g) in MeOH (20 mL) was heated to reflux for 2 h and then cooled to 0°C. The formed precipitate was collected by filtration to give the desired ester (1.78 g, 87%). $[MH]^+ = 206$.

Preparative Example 242



[0420] Step A

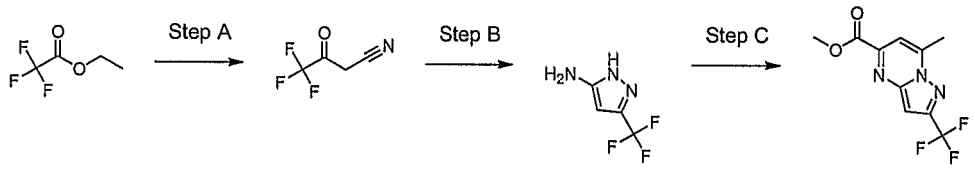
A mixture of commercially available 5-aminopyrazolone (5 g) and $POCl_3$ (50 mL) was heated to 210°C for 5 h, concentrated and quenched with MeOH (10 mL) at 0°C.

Purification by chromatography (silica, hexanes/EtOAc) afforded the desired product (293 mg, 5%). $[MH]^+ = 118$.

[0421] Step B

A mixture of the title compound from Step A above (117 mg) and methyl acetopyruvate (144 mg) in MeOH (5 mL) was heated to reflux for 2 h and then cooled to 0°C. The formed precipitate was collected by filtration to give the desired ester (200 mg, 89%). $[MH]^+ = 226$.

Preparative Example 243



[0422] Step A

Under a nitrogen atmosphere at 0°C was slowly added 1,4-dioxane (350 mL) to NaH (60% in mineral oil, 9.6 g) followed by the slow addition of CH_3CN (12.6 mL). The mixture was allowed to warm to room temperature before ethyl trifluoroacetate (23.8 mL) was added. The mixture was stirred at room temperature for 30 min, heated at 100°C for 5 h, cooled to room temperature and concentrated. The remaining solid was taken up in H_2O (400 mL), washed with Et_2O (300 mL), adjusted to pH ~2 with concentrated HCl and extracted with CH_2Cl_2 (300 mL). The CH_2Cl_2 extract was dried ($MgSO_4$), filtered and concentrated to give a brown liquid, which was not further purified (12.5 g, 74%). $[M-H]^- = 136$.

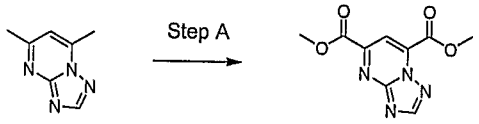
[0423] Step B

A mixture of the title compound from Step A above (12.5 g) and hydrazine monohydrate (6.0 g) in absolute EtOH (300 mL) was heated to reflux under a nitrogen atmosphere for 8 h, cooled to room temperature and concentrated. The remaining oil was taken up in CH_2Cl_2 (150 mL), washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to give the title compound (0.25 g, 2%). $[MH]^+ = 152$.

[0424] Step C

Using a microwave, a mixture of the title compound from Step B above (150 mg) and commercially available methyl acetopyruvate (150 mg) in MeOH (1 mL) in a sealed vial was heated at 120°C for 12 min, concentrated and purified by chromatography (silica, CH_2Cl_2) to give the title compound (0.15 g, 58%). $[MH]^+ = 260$.

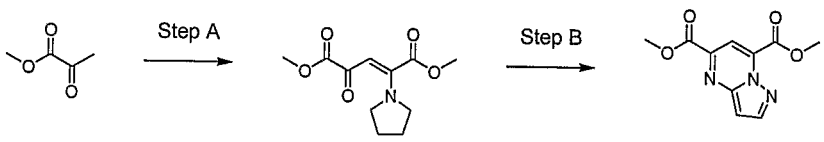
Preparative Example 244



[0425] Step A

To a suspension of selenium dioxide (9 g) in 1,4-dioxane (35 mL) was added commercially available 5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidine (3 g). The mixture was heated to reflux for 24 h, cooled to room temperature, filtered through a plug of celite® and concentrated. The remaining solid residue was taken up in MeOH (50 mL), oxone (7 g) was added and the mixture was heated to reflux for 24 h, cooled to room temperature, diluted with CH_2Cl_2 (50 mL), filtered through a plug of celite® and concentrated. The remaining residue was dissolved in a saturated solution of HCl in MeOH (150 mL), heated to reflux under a nitrogen atmosphere for 24 h, filtered through a medium porosity fritted glass funnel, concentrated and partially purified by chromatography (silica, CH_2Cl_2/MeOH) to give the title compound, which was not further purified (0.2 g, 4%). $[MH]^+ = 238$.

Preparative Example 245



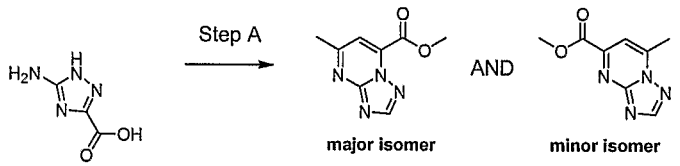
[0426] Step A

A solution of methyl pyruvate (13.6 mL) in ^{t}BuOMe (100 mL) was added dropwise to a cooled (–10°C) solution of pyrrolidine (12.6 mL) in ^{t}BuOMe (100 mL) over a period of 30 min. The mixture was stirred at –10°C for 15 min, then trimethylborate (8.0 mL) was

added dropwise over a period of 2 min and stirring at –10°C was continued for 2 h. NEt_3 (55 mL) was added, followed by the dropwise addition of a solution of methyl oxalylchloride (24.6 mL) in ^{t}BuOMe (100 mL) over a period of 30 min. The resulting thick slurry was stirred for 30 min and then diluted with saturated aqueous $NaHCO_3$ (250 mL) and CH_2Cl_2 (200 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were concentrated to give an oil, which was triturated with ^{t}BuOMe to afford the title compound as a yellowish solid (15.75 g, 45%). $[MH]^+ = 242$.

[0427] Step B

To mixture of the title compound from Step A above (6 g) and commercially available 2-aminopyrazole (2.1 g) in MeOH (10 mL) was added 3N aqueous HCl (3 mL). The mixture was heated to reflux overnight and cooled. The precipitated title compound was collected by filtration. The supernatant was concentrated and purified by chromatography (silica, hexane/EtOAc) to afford additional solid material, which was combined with the collected precipitate to give title compound (3.7 g, 60%). $[MH]^+ = 250$.**Preparative Example 246**



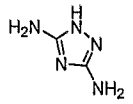
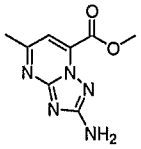
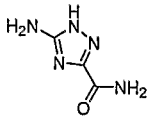
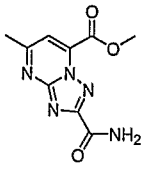
[0428] Step A

A mixture of commercially available 5-amino-1*H*-[1,2,4]triazole-3-carboxylic acid (20.3 g) and methyl acetopyruvate (20.0 g) in glacial AcOH (250 mL) was heated to 95°C for 3 h. The mixture was concentrated and diluted with saturated aqueous $NaHCO_3$ (200 mL) and CH_2Cl_2 (500 mL). The organic phase was separated, dried ($MgSO_4$), filtered and concentrated to give a pale orange mixture of regioisomers (80:20, 21.3 g, 80%). Recrystallization of the crude material from hot THF (110 mL) afforded the major isomer of the title compound (13.0 g, 49%). $[MH]^+ = 193$. The supernatant was concentrated and purified by chromatography (silica, hexanes/EtOAc) to afford the minor isomer of title compound. $[MH]^+ = 193$.

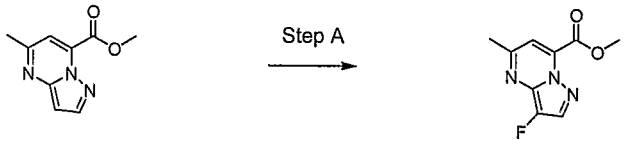
Preparative Examples 247-248

[0429] Following a similar procedure as described in the Preparative Example 246, except using the amines indicated in Table I-11 below, the following compounds were prepared.

Table I-11

Prep. Ex. #	amine	product	yield
247			96% $[MH]^+ = 208$
248			92% $[MH]^+ = 236$

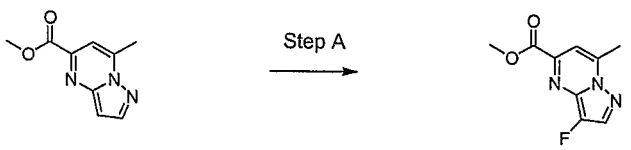
Preparative Example 249



[0430] Step A

To a solution of the minor isomer of the title compound from the Preparative Example 239, Step A (500 mg) in CH_3CN (10 mL) were added AcOH (2 mL) and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) [selectfluor®] (551 mg). The resulting mixture was stirred at 70°C for 7 h, cooled to room temperature, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound (149 mg, 27%). $[MH]^+ = 210$.

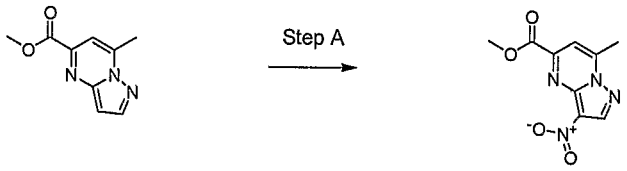
Preparative Example 250



[0431] Step A

To a suspension of the major isomer of the title compound from the Preparative Example 239, Step A (10.0 g) in H_2O (1.0 L) was added 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) [selectfluor®] (18.6 g). The resulting mixture was stirred at 50°C for 18 h, cooled to room temperature and extracted with CH_2Cl_2 (3 x 350 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/acetone) to afford the title compound (4.25 g, 39%). $[MH]^+ = 210$.

Preparative Example 251



[0432] Step A

To a stirred solution of $Bu_4N(NO_3)$ (1.39 g) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (579 μL). The resulting mixture was cooled to 0°C and added to an ice cooled solution of the major isomer of the title compound from the Preparative Example 239, Step A (796 mg) in CH_2Cl_2 (10 mL). The mixture was allowed to reach room temperature overnight, diluted with $CHCl_3$, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound (200 mg, 20%). $[MH]^+ = 237$.

Preparative Example 252



[0433] Step A

To a suspension of the minor isomer of the title compound from the Preparative Example 239, Step A (500 mg) in $CHCl_3$ (10 mL) was added *N*-bromosuccinimide (465 mg). The resulting mixture was heated to reflux for 1 h, cooled to room temperature, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound (599 mg, 85%). $[MH]^+ = 270/272$.

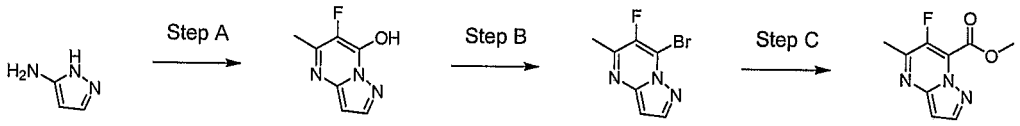
Preparative Example 253



[0434] Step A

A mixture of the minor isomer of title compound from the Preparative Example 239, Step A (100 mg) and *N*-chlorosuccinimide (77 mg) in CCl_4 (5 mL) was heated to reflux for 24 h, cooled, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound (98 mg, 83%). $[MH]^+ = 226$.

Preparative Example 254



[0435] Step A

A mixture of commercially available 2*H*-pyrazol-3-ylamine (2.0 g) and 2-fluoro-3-oxo-butyric acid methyl ester (4.4 g) in MeOH (15 mL) was heated at 80°C for 16 h and then cooled to room temperature. The formed precipitate was isolated by filtration and dried to afford the title compound (4.2 g, 84%). $[MH]^+ = 168$.

[0436] Step B

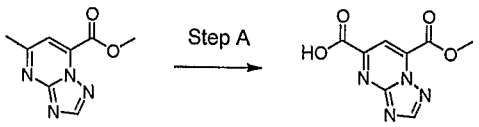
To a mixture of the title compound from Step A above (1.67 g) in CH_3CN (150 mL) were added K_2CO_3 (4.15 g) and $POBr_3$ (8.58 g). The mixture was heated to reflux for 16 h, concentrated, diluted with $CHCl_3$, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$),

filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a colorless solid (690 mg, 30%). $[MH]^+ = 230/232$.

[0437] Step C

The title compound from Step B above (28 mg) was treated similarly as described in the Preparative Example 103, Step A to afford the title compound (295 mg, 70%). $[MH]^+ = 210$.

Preparative Example 255



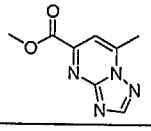
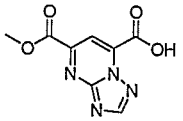
[0438] Step A

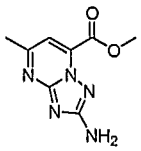
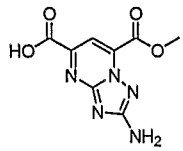
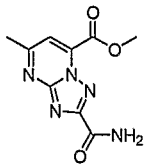
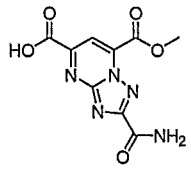
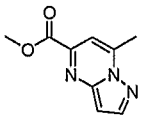
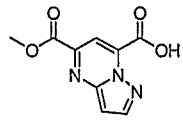
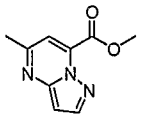
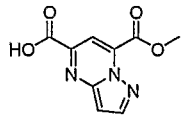
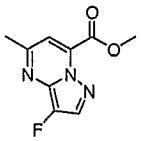
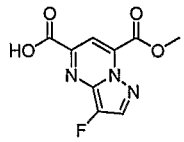
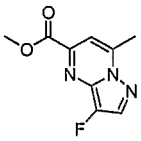
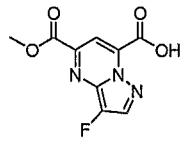
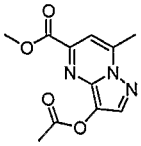
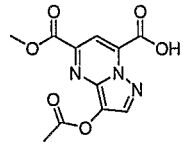
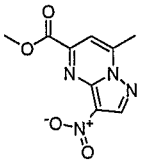
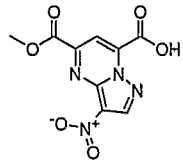
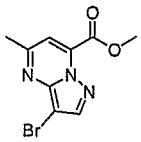
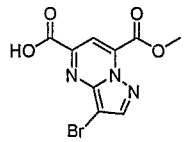
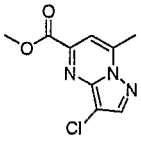
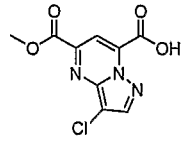
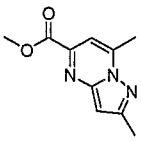
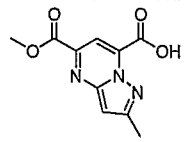
A mixture of the major isomer of title compound from the Preparative Example 246, Step A (1.34 g) and selenium dioxide (1.78 g) in 1,4-dioxane (20 mL) was heated to 120°C under closed atmosphere for 12 h, cooled and filtered through celite®. To the filtrate were added oxone (1.70 g) and H_2O (400 μL) and the resulting suspension was stirred at room temperature overnight. Concentration and purification by chromatography (silica, CH_2Cl_2/MeOH) afforded the title compound (1 g, 64%). $[MH]^+ = 223$.

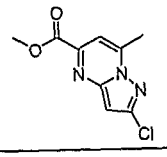
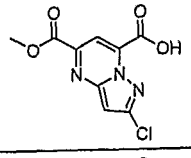
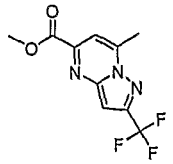
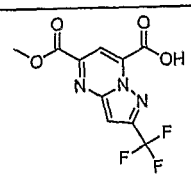
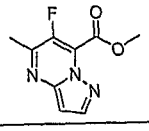
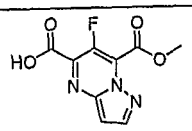
Preparative Examples 256-270

[0439] Following a similar procedure as described in the Preparative Example 255, except using the intermediates indicated in Table I-12 below, the following compounds were prepared.

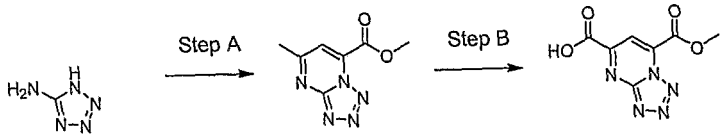
Table I-12

Prep. Ex. #	intermediate	product	yield
256			69% $[MH]^+ = 223$

Prep. Ex. #	intermediate	product	yield
257			70% $[MH]^+ = 238$
258			77% $[MH]^+ = 266$
259			34% $[MH]^+ = 222$
260			24% $[MH]^+ = 222$
261			60% $[MH]^+ = 240$
262			71% $[MH]^+ = 240$
263			87% $[MH]^+ = 280$
264			46% $[MH]^+ = 267$
265			n.d. $[MH]^+ = 300/302$
266			80% $[MH]^+ = 256$
267			55% $[MH]^+ = 236$

Prep. Ex. #	intermediate	product	yield
268			82% $[MH]^+ = 256$
269			68% $[MH]^+ = 290$
270			80% $[MH]^+ = 240$

Preparative Example 271



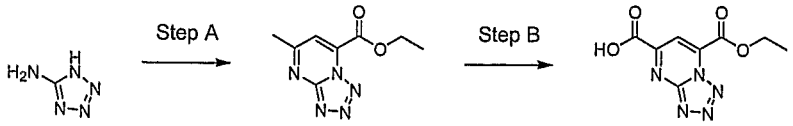
[0440] Step A

A suspension of commercially available methyl acetopyruvate (3.60 g) in H_2O (10 mL) was heated to 40°C, then a mixture of commercially available 1*H*-tetrazol-5-amine (2.10 g) and concentrated HCl (2 mL) in H_2O (4 mL) was added and the mixture was heated to reflux for 1 h, before it was cooled to 0°C. The formed precipitate was filtered off, washed wit H_2O, dried in vacuo and purified by flash chromatography (silica, CH_2Cl_2/acetone) to afford the title compound as a mixture of regioisomers (~91:9, 2.15 g, 45%). $[MH]^+ = 194$.

[0441] Step B

To a mixture of selenium dioxide (780 mg) in 1,4-dioxane (10 mL) was added dropwise a 5.5M solution of *tert*-butyl hydroperoxide in hexanes (5 mL). The mixture was stirred at room temperature for 30 min, then the title compound from Step A above (600 mg) was added and the mixture was heated to reflux for 24 h. The mixture was filtered through a plug of celite®, concentrated, diluted with H_2O (10 mL) and extracted with $CHCl_3$. The combined organic phases were dried ($MgSO_4$), filtered and concentrated to afford the crude title compound, which was used without further purification. $[MH]^+ = 224$.

Preparative Example 272



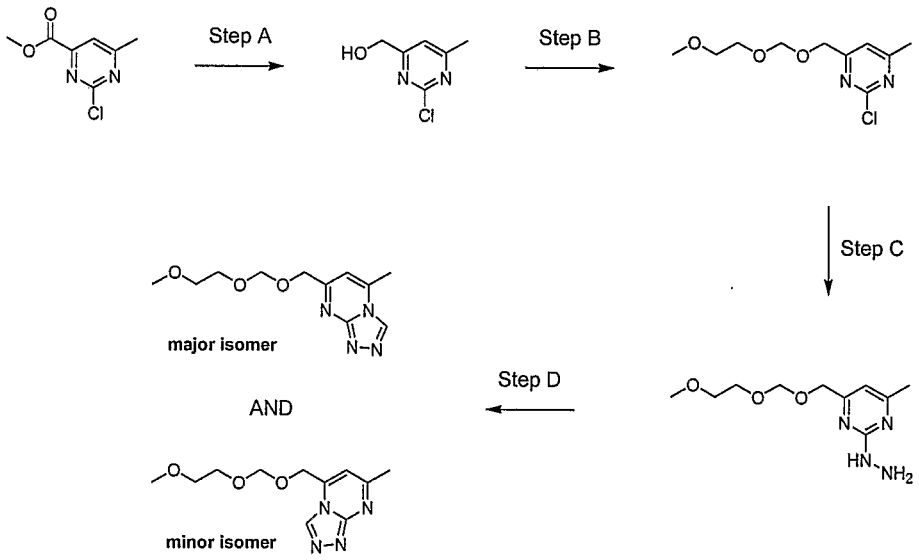
[0442] Step A

Commercially available 1*H*-tetrazol-5-amine (2.15 g) was treated similarly as described in the Preparative Example 271, Step A, except using ethyl acetopyruvate (4.00 g) to afford the title compound as a pale orange mixture of regioisomers (~75:25, 4.20 g, 80%). $[MH]^+ = 208$.

[0443] Step B

The title compound from Step B above (4.00 g) was treated similarly as described in the Preparative Example 271, Step B to afford the title compound as a orange red solid (1.30 g, 28%). $[MH]^+ = 238$

Preparative Example 273



[0444] Step A

To an ice cooled solution of commercially available 2-chloro-6-methyl-pyrimidine-4-carboxylic acid methyl ester (20.05 g) in MeOH (500 mL) was added $NaBH_4$ (8.10 g) in

small portions over a period of 3 h. The cooling bath was removed and the mixture was stirred at room temperature for 10 h. The mixture was poured into saturated aqueous NH_4Cl and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to afford the title compound as an off-white solid (17.26 g, >99%). $[MH]^+ = 159$.

[0445] Step B

To an ice cooled suspension of the title compound from Step A above (17.08 g) in CH_2Cl_2 (300 mL) were subsequently added $^iPr_2NEt$ (30 mL) and (2-methoxyethoxy)methyl chloride (13.5 mL). The mixture was stirred at room temperature for 12 h, additional $^iPr_2NEt$ (11 mL) and (2-methoxyethoxy)methyl chloride (6.1 mL) were added and stirring at room temperature was continued for 6 h. Then the mixture was concentrated and purified by chromatography (silica, hexane/EtOAc) to afford the title compound as a yellow oil (10.75 g, 42%). $[MH]^+ = 247$.

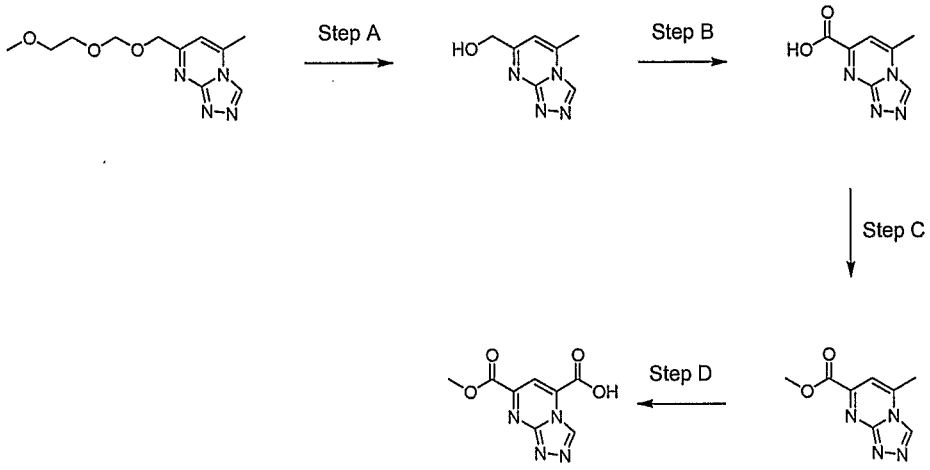
[0446] Step C

Under a nitrogen atmosphere a solution of the title compound from Step B above (10.75 g) in MeOH (60 mL) was added dropwise to a stirred solution of hydrazine hydrate (10.60 mL) in MeOH (300 mL) at 70°C. The mixture was stirred at 70°C for 14 h, cooled and concentrated. The remaining residue was diluted with CH_2Cl_2 (200 mL), filtered and concentrated to afford the title compound as a yellow oil (10.00 g, 95%). $[MH]^+ = 243$.

[0447] Step D

A suspension of the title compound from Step C above (9.50 g) in $(EtO)_3CH$ (200 mL) was heated to reflux for 6 h. Then AcOH (5 mL) was added at heating to reflux was continued for 6 h. The mixture was cooled, concentrated and purified by chromatography (silica) to afford major isomer (7.05 g, 71%) and the minor isomer (2.35 g, 24%) of the title compound. $[MH]^+ = 253$.

Preparative Example 274



[0448] Step A

To a solution of the major isomer of title compound from the Preparative Example 273, Step D (9.40 g) in THF (200 mL) was added a 4M solution of HCl in 1,4-dioxane (37 mL). The mixture was stirred at room temperature for 2 h and then concentrated to afford the title compound (8.53 g, >99%). $[MH]^+ = 165$.

[0449] Step B

The title compound from Step A above (8.53 g) and Na_2CO_3 (4.26 g) were dissolved in H_2O (250 mL). The suspension was heated to 50°C and $KMnO_4$ (8.13 g) was added in small portions over a period of 30 min. The mixture was stirred at 50°C for 2 h, cooled to room temperature, filtered through a pad of celite® and concentrated to afford the crude title compound, which was used without further purification (13.42 g). $[MH]^+ = 179$.

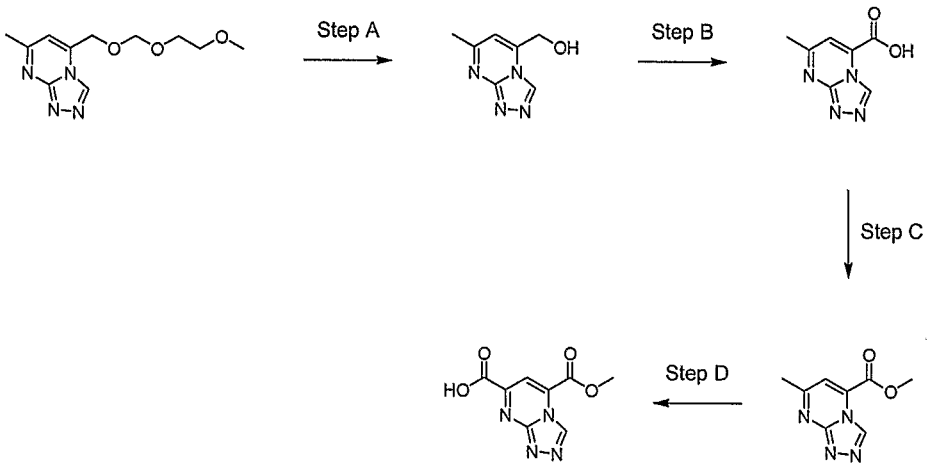
[0450] Step C

$SOCl_2$ (10.9 mL) was added dropwise to an ice cooled suspension of the title compound from Step B above (13.4 g) in MeOH (400 mL). The cooling bath was removed and the mixture was stirred at room temperature for 12 h. Concentration and purification by chromatography (silica, CH_2Cl_2/MeOH) afforded the title compound as an orange solid (2.23 g, 16%). $[MH]^+ = 193$.

[0451] Step D

A mixture of the title compound from Step C above (1.21 g) and selenium dioxide (1.40 g) in 1,4-dioxane (20 mL) was heated to 70°C for 4 h. Cooling to room temperature, filtration through a pad of celite® and concentration afforded the crude title compound as a red solid, which was used without further purification (1.4 g). $[MH]^+ = 223$.

Preparative Example 275



[0452] Step A

The minor isomer of title compound from the Preparative Example 273, Step D (2.35 g) was treated similarly as described in the Preparative Example 274, Step A to afford the title compound (1.53 g, >99%). $[MH]^+ = 165$.

[0453] Step B

The title compound from Step A above (1.53 g) was treated similarly as described in the Preparative Example 274, Step B to afford the title compound. $[MH]^+ = 179$.

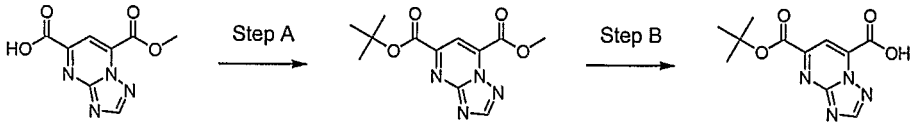
[0454] Step C

The title compound from Step B above was treated similarly as described in the Preparative Example 274, Step C to afford the title compound. $[MH]^+ = 193$.

[0455] Step D

The title compound from Step C above was treated similarly as described in the Preparative Example 274, Step D to afford the title compound. $[MH]^+ = 223$.

Preparative Example 276



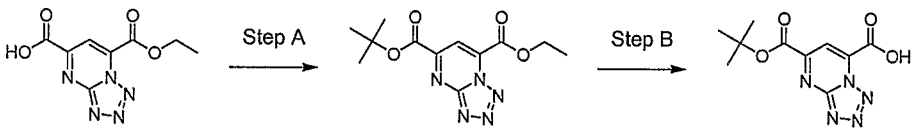
[0456] Step A

A suspension of the title compound from the Preparative Example 255, Step A (2.22 g) in dry toluene (15 mL) was placed in a preheated oil bath (~80°C). Then *N,N*-dimethylformamide di-*tert*-butyl acetal (9.60 mL) was added carefully over a period of ~10 min and the resulting black/brown mixture was stirred at ~ 80°C for 1 h. The mixture was cooled to room temperature, diluted with EtOAc (150 mL), washed with H_2O (2 x 150 mL) and saturated aqueous NaCl (150 mL), dried ($MgSO_4$), filtered, concentrated and purified by flash chromatography (silica, cyclohexane/EtOAc) to afford the title compound (1.39 g, 50%). $[MH]^+ = 279$.

[0457] Step B

To a solution of the title compound from Step A above (1.39 g) in dry 1,2-dichloroethane (50 mL) was added trimethyltin hydroxide (1.01 g). The resulting yellow suspension was placed in a preheated oil bath (~80°C) and stirred at this temperature for 2 h. The mixture was cooled to room temperature, diluted with EtOAc (250 mL), washed with 5% aqueous HCl (2 x 250 mL) and saturated aqueous NaCl (250 mL), dried ($MgSO_4$), filtered, concentrated and vacuum dried for ~15 h to afford a beige solid, which was used without further purification (756 mg, 57%). $[MH]^+ = 265$.

Preparative Example 277



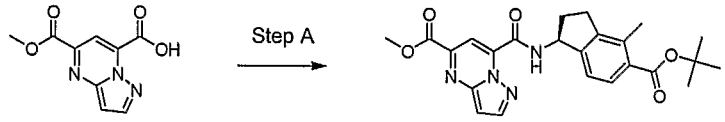
[0458] Step A

The title compound from the Preparative Example 272, Step B (2.37 g) was treated similarly as described in the Preparative Example 276, Step A to afford the title compound (1.68 g, 57%). $[MH]^+ = 294$.

[0459] Step B

The title compound from Step A above (1.36 g) was treated similarly as described in the Preparative Example 276, Step B to afford the title compound as a beige solid (1.20 g, 97%). $[MH]^+ = 266$.

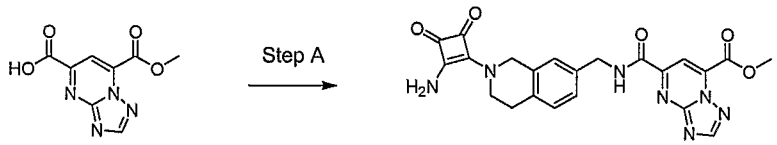
Preparative Example 278



[0460] Step A

To a solution of the title compound from the Preparative Example 259 (94 mg) in DMF (3 mL) were added the title compound from the Preparative Example 7, Step D (94 mg), PyBrOP (216 mg) and $^iPr_2NEt$ (123 μL). The mixture was stirred at room temperature for 2 h, concentrated and purified by chromatography (silica, CH_2Cl_2/acetone) to afford the title compound (60 mg, 37%). $[MH]^+ = 451$.

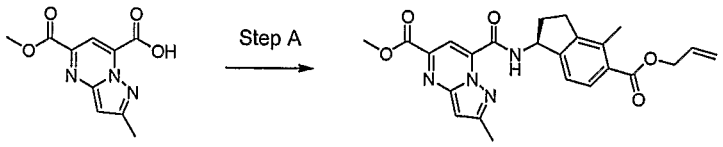
Preparative Example 279



[0461] Step A

To an ice cooled solution of the title compound from the Preparative Example 255, Step A (250 mg) and the title compound from the Preparative Example 214, Step A (329 mg) in DMF (10 mL) were added *N*-methylmorpholine (170 μL), HATU (570 mg) and HOAt (204 mg). The mixture was stirred overnight while warming to room temperature and then concentrated. The remaining residue was dissolved in $CHCl_3$, washed with saturated aqueous $NaHCO_3$, 1N aqueous HCl and saturated aqueous NaCl, dried ($MgSO_4$), filtered, absorbed on silica and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a yellow/brown gummy solid (177 mg, 35%). $[MH]^+ = 462$.

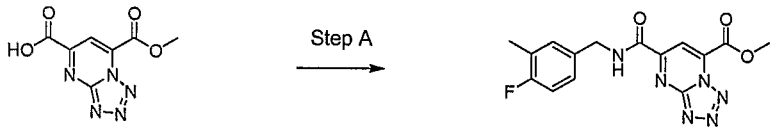
Preparative Example 280



[0462] Step A

To a solution of the title compound from the Preparative Example 267 (236 mg) in anhydrous CH_2Cl_2 (5 mL) was added oxalyl chloride (0.32 mL) at 0°C, followed by the addition of anhydrous DMF (0.1 mL). The mixture was allowed to warm to room temperature, stirred for 1 h and concentrated. To the remaining reddish solid residue was added anhydrous CH_2Cl_2 (5 mL) at 0°C, followed by the addition of a solution of the title compound from the Preparative Example 138 (231 mg) and NEt_3 (0.42 mL) in anhydrous CH_2Cl_2 (5 mL). The mixture was allowed to warm to room temperature, stirred overnight, concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to give the desired product (150 mg, 34%). $[MH]^+ = 449$.

Preparative Example 281



[0463] Step A

A solution of the title compound from the Preparative Example 271, Step B (~670 mg), PyBOP (2.35 g) and $^iPr_2NEt$ (780 μL) in DMF (5 mL) was stirred at room temperature for 1 h. Commercially available 4-fluoro-3-methyl benzylamine (500 mg) and $^iPr_2NEt$ (780 μL) were added and stirring at room temperature was continued overnight. The mixture was concentrated, diluted with EtOAc, washed with H_2O and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/acetone) to afford the title compound as a single regioisomer (200 mg, 19% over two steps). $[MH]^+ = 345$.

Preparative Example 282



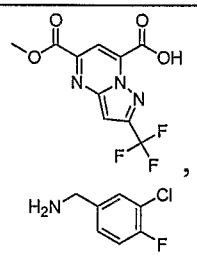
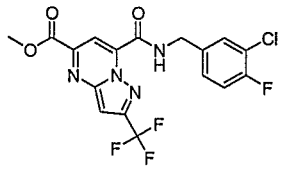
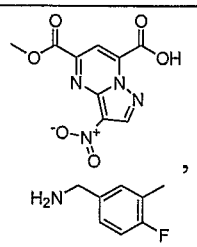
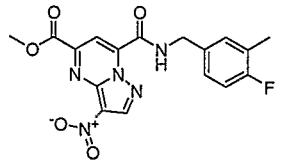
[0464] Step A

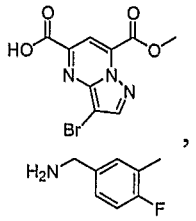
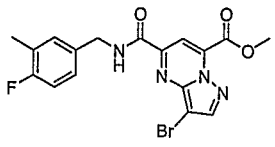
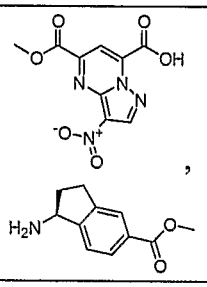
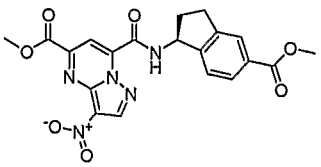
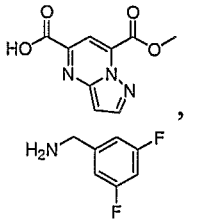
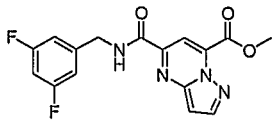
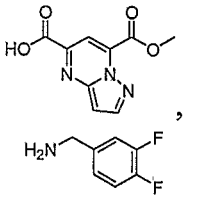
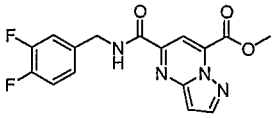
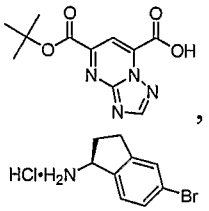
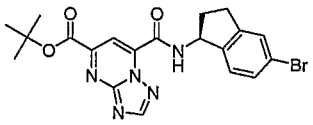
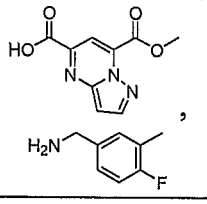
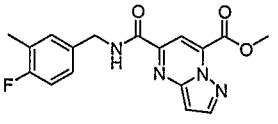
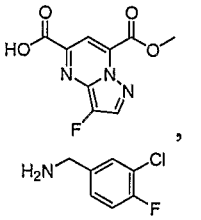
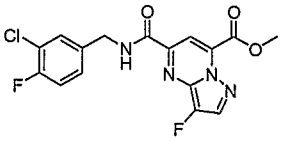
To a solution of the title compound from the Preparative Example 260 (506 mg) and the title compound from the Preparative Example 161 (555 mg) in DMF (15 mL) were added *N*-methylmorpholine (250 μL), EDCI (530 mg) and HOAt (327 mg). The mixture was stirred overnight and then concentrated. The remaining residue was dissolved in $CHCl_3$, washed with 10% aqueous citric acid and saturated aqueous NaCl, dried ($MgSO_4$), filtered, absorbed on silica and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as an orange solid (208 mg, 24%). $[MH]^+ = 382$.

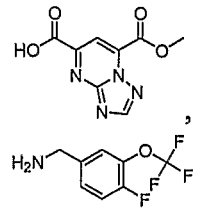
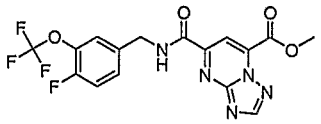
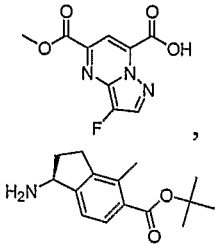
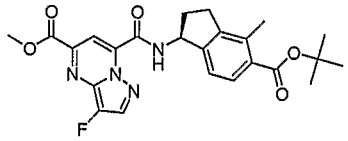
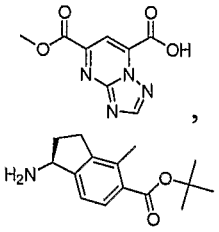
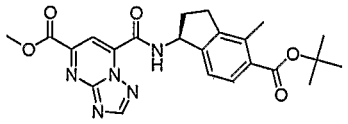
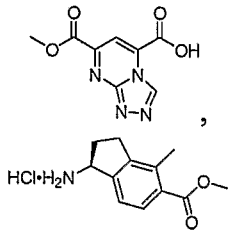
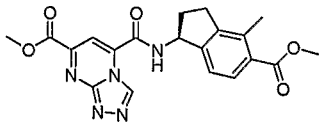
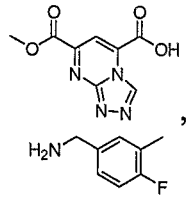
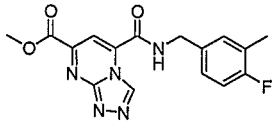
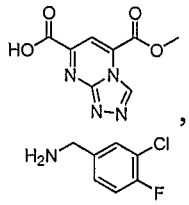
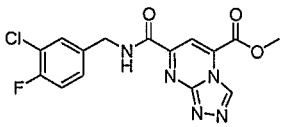
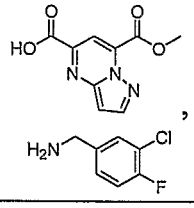
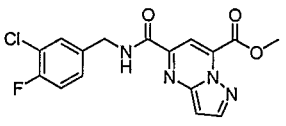
Preparative Examples 283-320

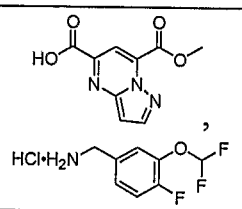
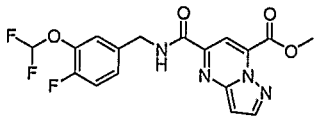
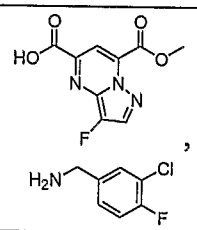
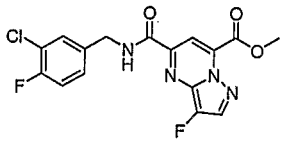
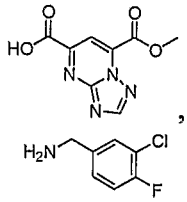
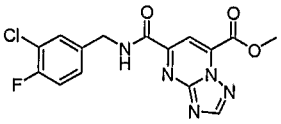
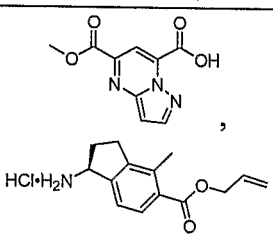
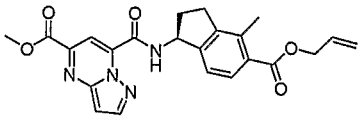
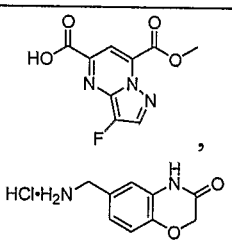
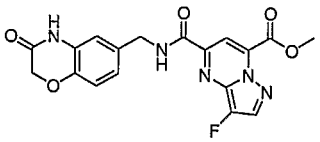
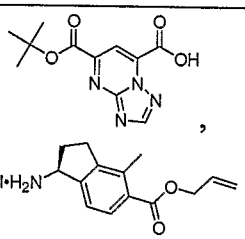
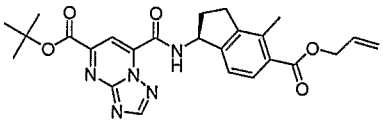
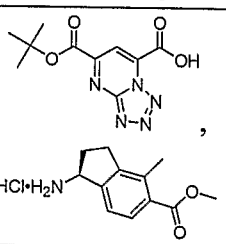
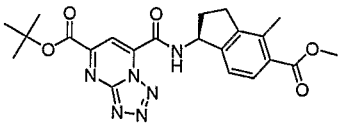
[0465] Following similar procedures as described in the Preparative Examples 279 (method A), 280 (method B), 281 (method C), 278 (method D) or 282 (method E), except using the acids and amines indicated in Table I-13 below, the following compounds were prepared.

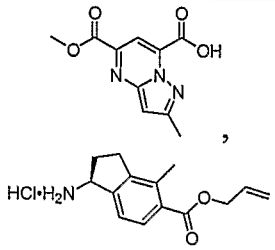
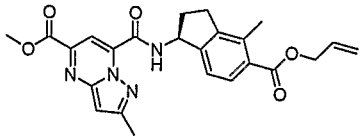
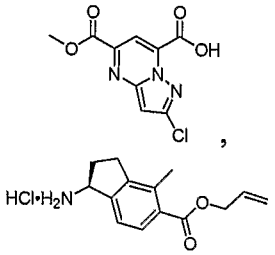
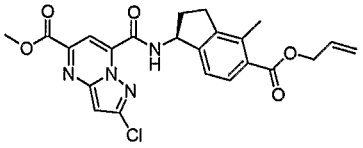
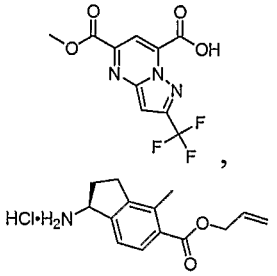
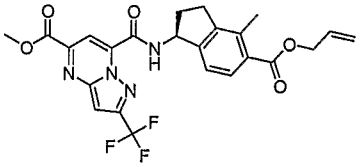
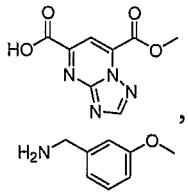
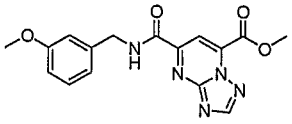
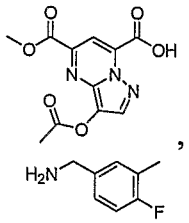
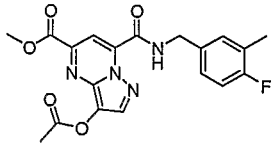
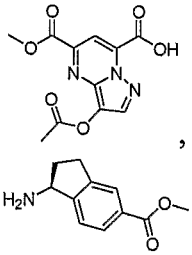
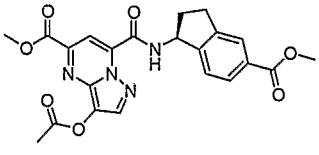
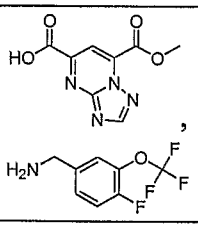
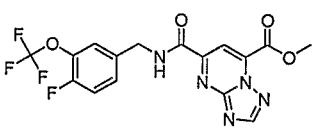
Table I-13

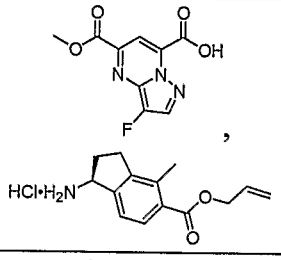
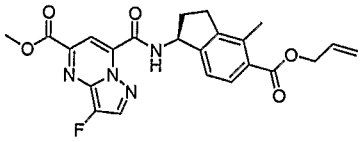
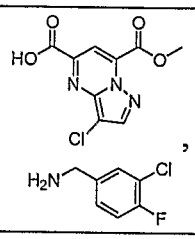
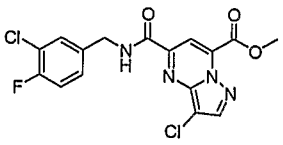
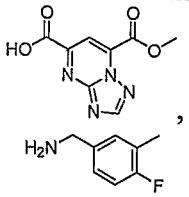
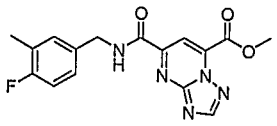
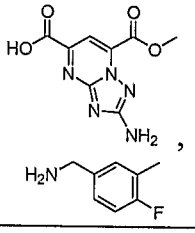
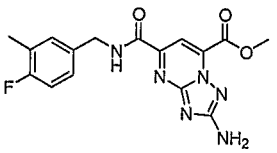
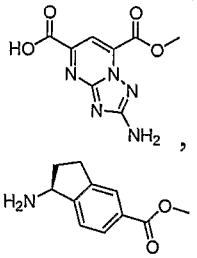
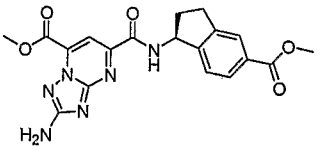
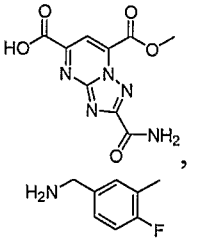
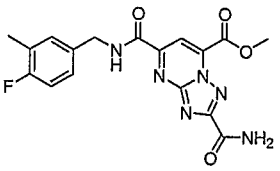
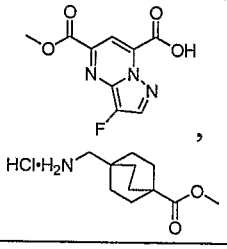
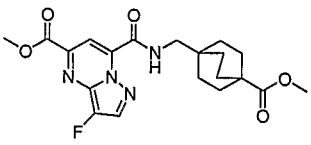
Prep. Ex. #	acid, amine	product	method, yield
283			B, 36% $[MH]^+ = 431$
284			C, 47% $[MH]^+ = 388$

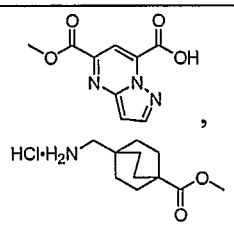
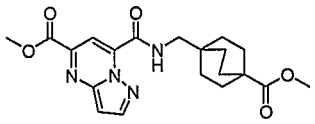
Prep. Ex. #	acid, amine	product	method, yield
285			C, n.d. $[MH]^+ = 421/423$
286			C, 33% $[MH]^+ = 440$
287			A, 41% $[MH]^+ = 347$
288			A, 44% $[MH]^+ = 347$
289			A, 76% $[MH]^+ = 458/460$
290			D, 11% $[MH]^+ = 343$
291			A, 83% $[MH]^+ = 381$

Prep. Ex. #	acid, amine	product	method, yield
292			A, 73% $[MH]^+ = 414$
293			A, 32% $[MNa]^+ = 491$
294			B, 76% $[M-H]^- = 452$
295			A, 7% (over 2 steps), $[MH]^+ = 410$
296			A, n.d. $[MH]^+ = 344$
297			B, 34% $[MH]^+ = 364$
298			B, 72% $[MH]^+ = 363$

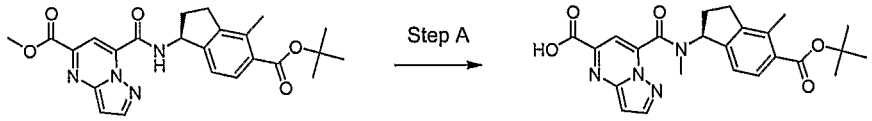
Prep. Ex. #	acid, amine	product	method, yield
299			A, 37% $[MH]^+ = 395$
300			A, 79% $[MH]^+ = 381$
301			A, 71% $[MH]^+ = 364$
302			A, 43% $[MH]^+ = 435$
303			E, 82% $[MH]^+ = 400$
304			A, 67% $[MNa]^+ = 500$
305			A, 73% $[MNa]^+ = 475$

Prep. Ex. #	acid, amine	product	method, yield
306			B, 34% $[MH]^+ = 449$
307			B, 34% $[MNa]^+ = 491$
308			B, 73% $[M-H]^- = 501$
309			A, 20% $[MH]^+ = 342$
310			A, 21% $[MH]^+ = 401$
311			A, 10% $[MH]^+ = 453$
312			A, 73% $[MH]^+ = 414$

Prep. Ex. #	acid, amine	product	method, yield
313			A, 71% $[MH]^+ = 453$
314			A, >99% $[MH]^+ = 397$
315			A, 70% $[MH]^+ = 344$
316			A, 33% $[MH]^+ = 359$
317			A, 54% $[MH]^+ = 411$
318			A, 60% $[MH]^+ = 387$
319			A, 47% $[MH]^+ = 419$

Prep. Ex. #	acid, amine	product	method, yield
320			A, 29% $[MH]^+ = 401$

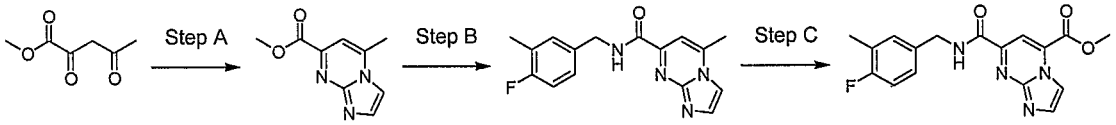
Preparative Example 321



[0466] Step A

To an ice cooled solution of the title compound from the Preparative Example 278, Step A (75 mg) in dry THF (10 mL) were successively added NaH (95%, 10 mg) and methyl iodide (250 μL). The cooling bath was removed and the resulting mixture was stirred at room temperature for 2 h. Concentration and purification by chromatography (silica, $CHCl_3$/MeOH) afforded the title compound as a colorless solid (52 mg, 69%). $[MNa]^+ = 473$.

Preparative Example 322



[0467] Step A

A mixture of commercially available 2-aminoimidazole sulfate (1.0 g), NH_4OAc (1.2 g) and methyl acetopyruvate (1.1 g) in AcOH (10 mL) was stirred at 120°C for 3 h, then absorbed on silica and purified by chromatography (silica, EtOAc/MeOH) to give an off-white solid (396 mg, 14%). $[MH]^+ = 192$.

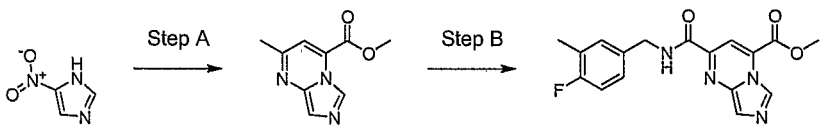
[0468] Step B

A solution of the title compound from Step A above (14 mg) in THF (100 μL), MeOH (100 μL), and 1N aqueous LiOH (80 μL) was stirred at 0°C for 2 h and then concentrated to give a yellow residue. $[MH]^+ = 178$. A mixture of this residue, PyBOP (42 mg), 4-fluoro-3-methyl-benzylamine (11 mg), and NEt_3 (20 μL) in DMF (200 μL) and THF (400 μL) was stirred for 4 h, then absorbed on silica and purified by chromatography (silica, EtOAc/MeOH) to give an off-white solid (12 mg, 55%). $[MH]^+ = 299$.

[0469] Step C

A mixture of the title compound from Step B above (100 mg) and selenium dioxide (93 mg) in dioxane (1.5 mL) was stirred at 80°C for 2 h. The mixture was cooled to room temperature and filtered through celite®. The filter cake was washed with dioxane (3 x 1 mL). To the supernatant were added oxone (206 mg) and H_2O (100 μL) and the resulting mixture was stirred for 4 h and then filtered. The supernatant was concentrated and then stirred in a premixed solution of acetyl chloride (100 μL) in MeOH (2 mL) in a sealed vial for 3 h at 65°C. The solution was absorbed on silica and purified by chromatography (silica, hexanes/EtOAc) to give a yellow solid (40 mg, 35%). $[MH]^+ = 343$.

Preparative Example 323



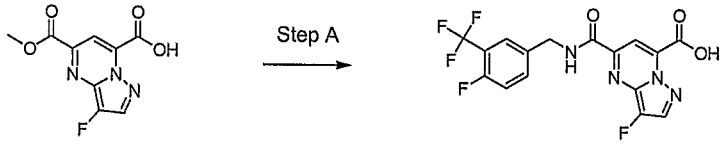
[0470] Step A

A mixture of commercially available 4-nitroimidazole (5 g) and Pd/C (10wt%, 500 mg) in a premixed solution of acetyl chloride (4 mL) in MeOH (100 mL) was hydrogenated in a Parr shaker at 35 psi for 5 h. The mixture was filtered through celite® and concentrated to give a black oil. $[MH]^+ = 115$. This oil and methyl acetylpyruvate (6.4 g) were stirred in AcOH (70 mL) and MeOH (70 mL) at 65°C for 18 h. The resulting mixture was absorbed on silica and purified by chromatography (silica, CH_2Cl_2/MeOH). Further purification of the resulting residue by chromatography (silica, EtOAc) afforded an orange solid (120 mg, 1.4%). $[MH]^+ = 192$.

[0471] Step B

A mixture of the title compound from Step A above (50 mg) and selenium dioxide (116 mg) in dioxane (1 mL) was heated to 130°C in a sealed tube for 6 h, cooled and filtered through celite®. The supernatant was concentrated to give a orange residue. $[MH]^+ = 222$. This residue was stirred with 4-fluoro-3-methyl-benzylamine (27 μL), PyBOP (150 mg), and NEt_3 (73 μL) in THF (2 mL) for 3 h, absorbed on silica and purified by chromatography (silica, hexanes/EtOAc) to give a yellow solid (22 mg, 24%). $[MH]^+ = 343$.

Preparative Example 324



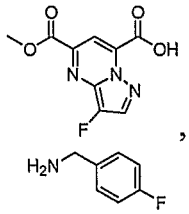
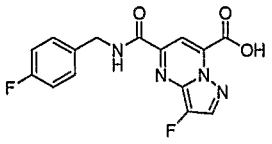
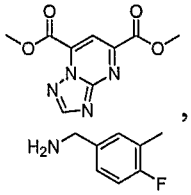
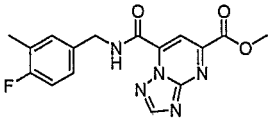
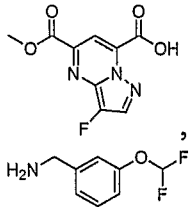
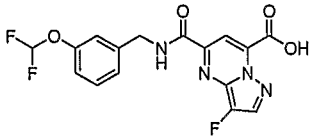
[0472] Step A

A solution of the title compound from the Preparative Example 262 (0.5 g) and 4-fluoro-3-trifluoromethylbenzyl amine (1.6 g) in DMF (2.5 mL) was stirred at 48°C for 10 h and then concentrated to an oil. The oil was taken up in EtOAc (120 mL), washed with 1N aqueous HCl (2 x 70 mL) and saturated aqueous NaCl (70 mL), dried ($MgSO_4$), filtered and concentrated. The remaining solid was washed with hexanes/Et_2O (1:1) and MeOH to give a yellow solid (0.31 g, 35%). $[MH]^+ = 401$.

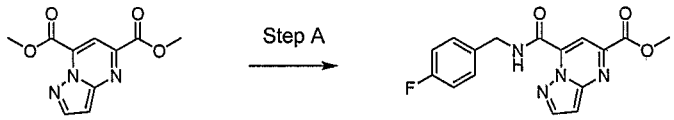
Preparative Examples 325-327

[0473] Following a similar procedure as described in the Preparative Example 324, except using the acids and amines indicated in Table I-14 below, the following compounds were prepared.

Table I-14

Prep. Ex. #	acid, amine	product	yield
325			n.d. $[MNa]^+ = 355$
326	 (0.5 eq.)		33% $[MH]^+ = 344$
327			65% $[MH]^+ = 381$

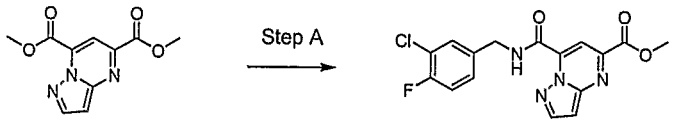
Preparative Example 328



[0474] Step A

A mixture of the title compound from the Preparative Example 245, Step B (10 mg), commercially available 4-fluorobenzylamine (5.3 mg) and scandium triflate (1 mg) in anhydrous DMF (1 mL) was heated to 60°C for 12 h, concentrated and purified by chromatography (silica) to afford the title compound as a yellow solid (11.5 mg, 83%). $[MH]^+ = 329$.

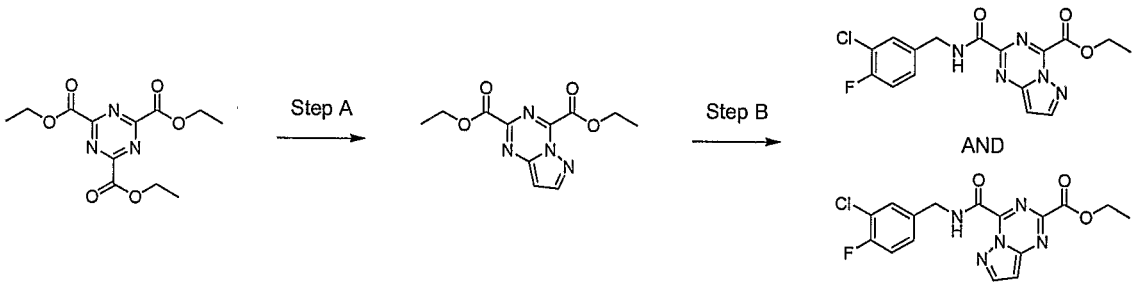
Preparative Example 329



[0475] Step A

The title compound from the Preparative Example 245, Step B (10 mg) was treated similarly as described in the Preparative Example 328, Step A, except using commercially available 3-chloro-4-fluorobenzylamine instead of 4-fluorobenzylamine to afford the title compound as a yellow solid (11.5 mg, 79%). $[MH]^+ = 363$.

Preparative Example 330



[0476] Step A

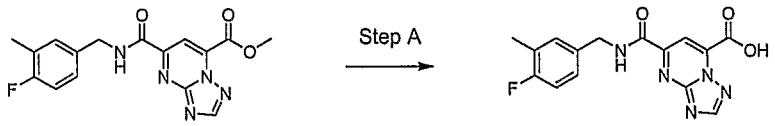
Under an argon atmosphere a solution of commercially available [1,3,5]triazine-2,4,6-tricarboxylic acid triethyl ester (818 mg) and 3-aminopyrazole (460 mg) in dry DMF (8 mL) was heated to 100°C overnight and then concentrated. The remaining residue was dissolved in $CHCl_3$, washed with 10% aqueous citric acid and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a colorless solid (409 mg, 56%). $[MH]^+ = 265$.

[0477] Step B

A mixture of the title compound from Step A above (203 mg) and commercially available 3-chloro-4-fluorobenzylamine (160 mg) in dry DMF (3 mL) was heated to 70°C overnight and concentrated. The remaining residue was dissolved in $CHCl_3$, washed with 10% aqueous citric acid and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by preparative thin layer chromatography (silica, CH_2Cl_2/MeOH) to afford the

title compound from the Example 286 and the separated regioisomers of the title compound. $[MH]^+ = 378$.

Preparative Example 331



[0478] Step A

To a solution of NaOH (24 mg) in dry MeOH (3.2 mL) was added the title compound from the Preparative Example 315 (170 mg). The resulting suspension was stirred at room temperature for 1 h, acidified with 1N aqueous HCl and concentrated. The remaining residue was dissolved in EtOAc, washed with 1N aqueous HCl, dried ($MgSO_4$), filtered and concentrated to afford the title compound (130 mg, 80%). $[MH]^+ = 330$.

Preparative Example 332



[0479] Step A

To a solution of the title compound from the Preparative Example 280, Step A (45 mg) in dioxane (3 mL) was added 1M aqueous LiOH (0.12 mL). The resulting mixture was stirred at room temperature for 2 h, adjusted to pH 2 and concentrated to give a red solid, which was used without further purification (43 mg, 99%). $[MH]^+ = 435$.

Preparative Example 333



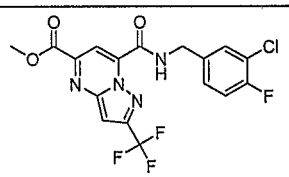
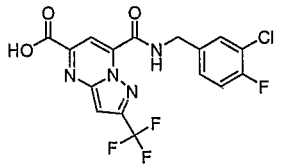
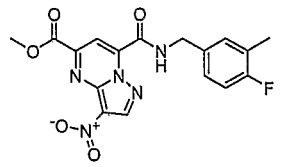
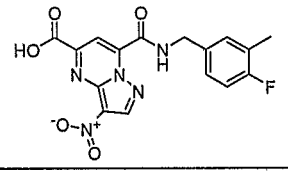
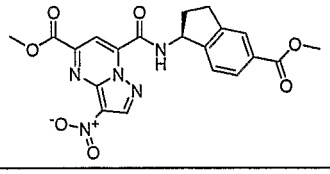
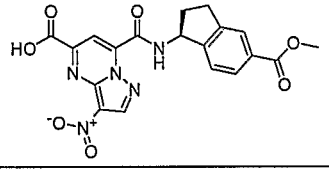
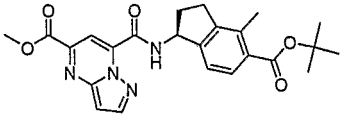
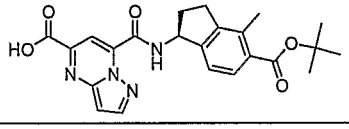
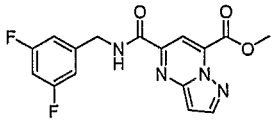
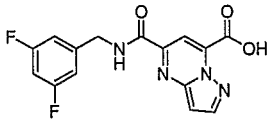
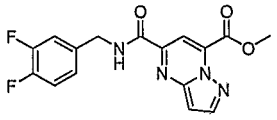
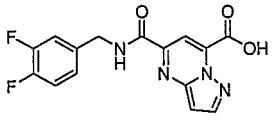
[0480] Step A

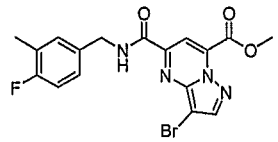
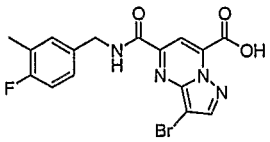
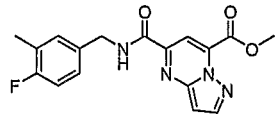
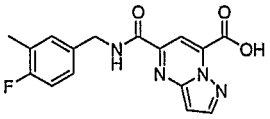
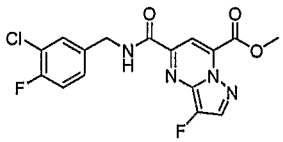
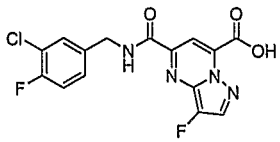
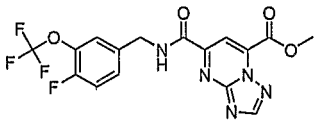
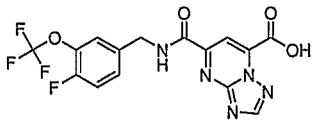
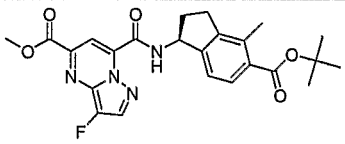
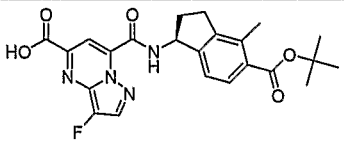
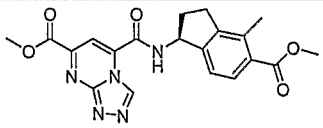
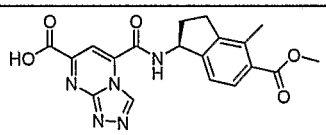
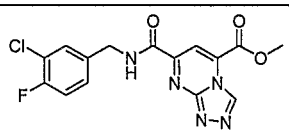
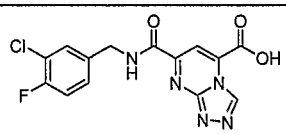
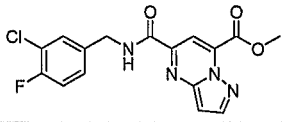
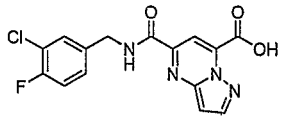
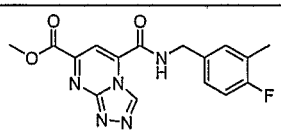
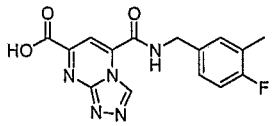
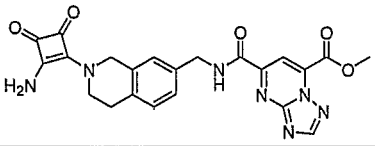
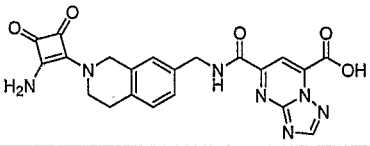
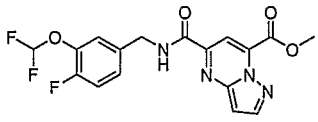
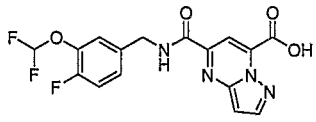
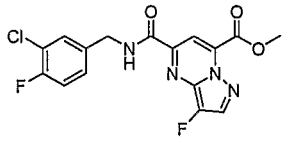
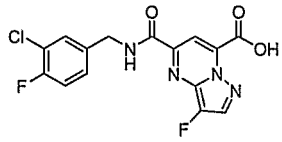
A mixture of the title compound from the Preparative Example 281, Step A (23 mg) and trimethyltin hydroxide (30 mg) in 1,2-dichloroethane (2 mL) was heated at 80°C for 3 h, concentrated, diluted with EtOAc (5 mL), washed with 10% aqueous $KHSO_4$ (5 mL) and saturated aqueous NaCl (5 mL), dried ($MgSO_4$), filtered and concentrated to afford the crude title compound (22 mg, 95%). $[MH]^+ = 331$.

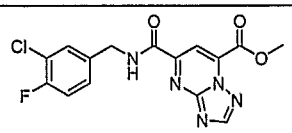
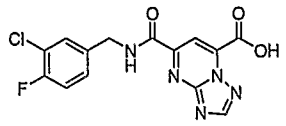
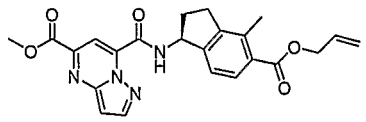
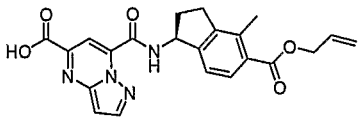
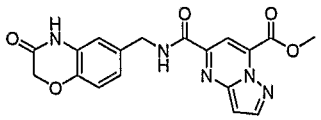
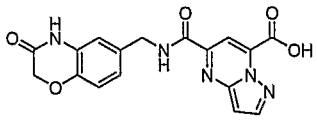
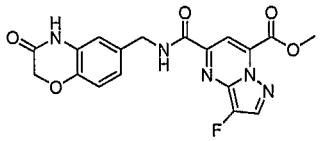
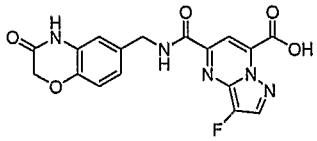
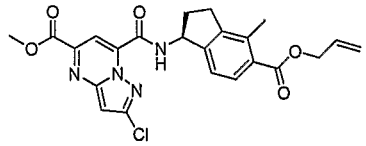
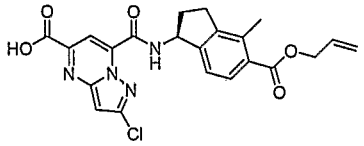
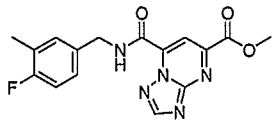
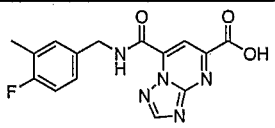
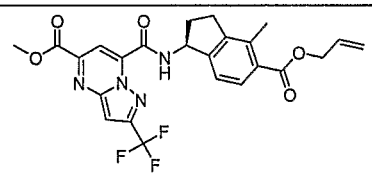
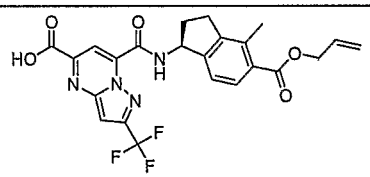
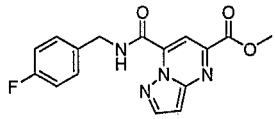
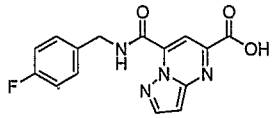
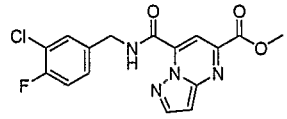
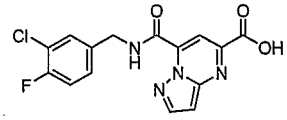
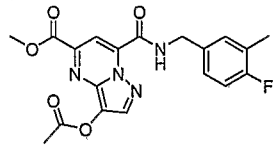
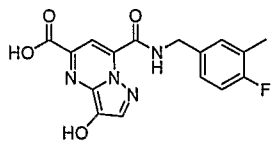
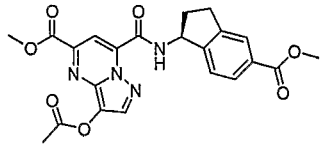
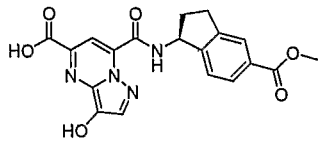
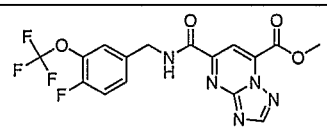
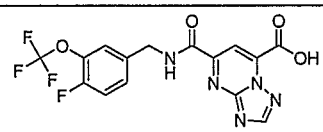
Preparative Examples 334-372

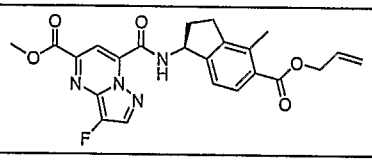
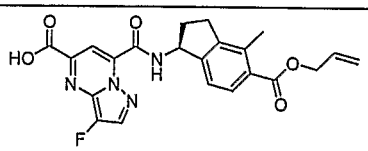
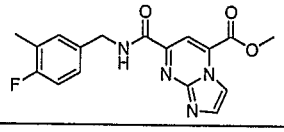
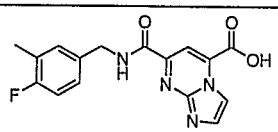
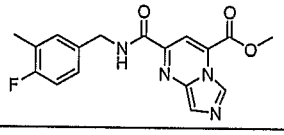
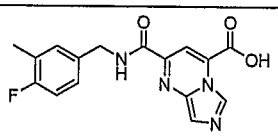
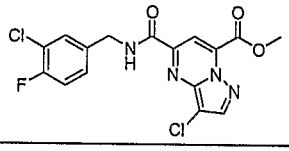
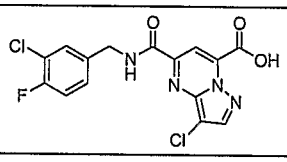
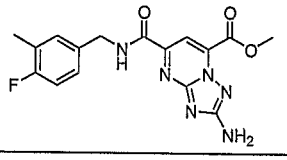
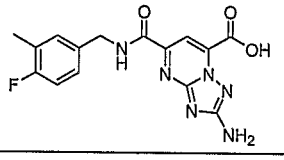
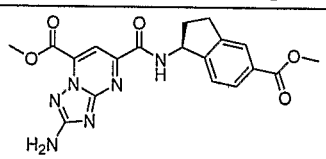
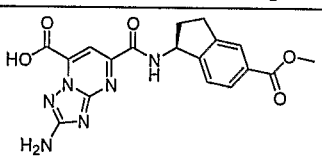
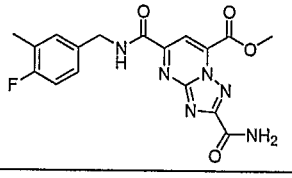
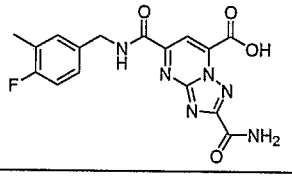
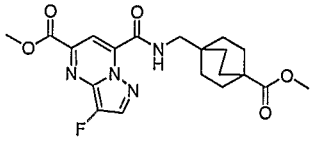
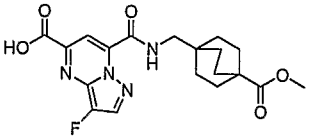
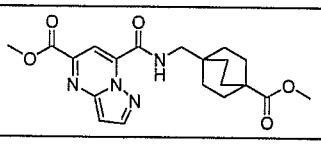
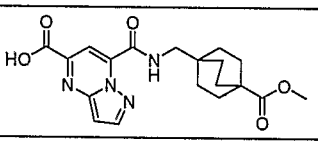
[0481] Following similar procedures as described in the Preparative Examples 331 (method A), 332 (method B) or 333 (method C), except using the esters indicated in Table I-15 below, the following compounds were prepared.

Table I-15

Prep. Ex. #	ester	product	method, yield
334			B, >99% $[MH]^+ = 415$
335			C, 97% $[MH]^+ = 374$
336			C, 95% $[MNa]^+ = 462$
337			A, 98% $[MH]^+ = 437$
338			A, 78% $[MH]^+ = 333$
339			A, 93% $[MH]^+ = 333$

Prep. Ex. #	ester	product	method, yield
340			A, n.d. $[MH]^+ = 407/409$
341			A, 98% $[MH]^+ = 329$
342			A, 96% $[MH]^+ = 367$
343			B, 61% $[MH]^+ = 400$
344			A, 96% $[MNa]^+ = 477$
345			C, n.d. $[MH]^+ = 396$
346			B, 83% $[MH]^+ = 350$
347			B, 97% $[MH]^+ = 349$
348			B, n.d. $[MH]^+ = 330$
349			A, 67% $[MH]^+ = 448$
350			A, 91% $[MH]^+ = 381$
351			A, >99% $[MH]^+ = 367$

Prep. Ex. #	ester	product	method, yield
352			B, 85% $[MH]^+ = 350$
353			A, 93% $[MH]^+ = 421$
354			B, 96% $[MH]^+ = 368$
355			B, 82% $[MH]^+ = 386$
356			B, 98% $[MH]^+ = 455$
357			B, >99% $[MH]^+ = 330$
358			B, >99% $[MH]^+ = 489$
359			A, n.d. $[MH]^+ = 315$
360			A, 18% $[MH]^+ = 349$
361			B, n.d. $[MH]^+ = 345$
362			C, n.d. $[MH]^+ = 397$
363			B, 61% $[MH]^+ = 414$

Prep. Ex. #	ester	product	method, yield
364			B, >99% $[MH]^+ = 439$
365			B, n.d. $[MH]^+ = 329$
366			B, n.d. $[MH]^+ = 329$
367			A, >99% $[MH]^+ = 383$
368			A, n.d. $[MH]^+ = 345$
369			A, n.d. $[MH]^+ = 397$
370			A, n.d. $[MH]^+ = 373$
371			A, 95% $[MH]^+ = 405$
372			A, 95% $[MH]^+ = 387$

Preparative Example 373



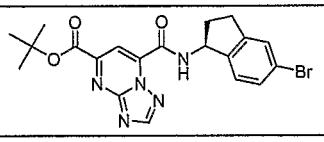
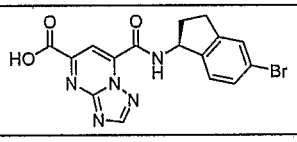
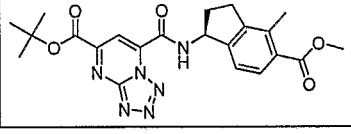
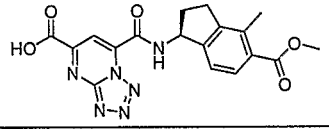
[0482] Step A

The title compound from the Preparative Example 304 (142 mg) was dissolved in trifluoroacetic acid/H_2O (9:1, 1.5 mL), stirred at room temperature for 1 h and concentrated by co-evaporation with toluene (3 x 10 mL) to yield a citreous/white solid, which was used without further purification (114 mg, 91%). $[MNa]^+ = 445$.

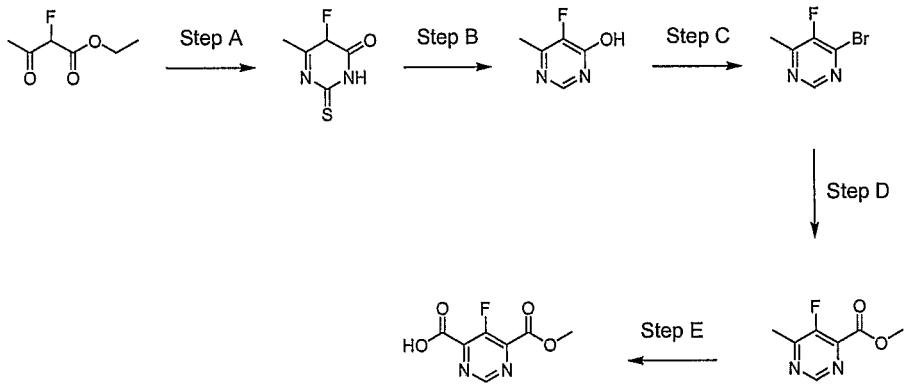
Preparative Examples 374-375

[0483] Following a similar procedure as described in the Preparative Example 373, except using the esters indicated in Table I-16 below, the following compounds were prepared.

Table I-16

Prep. Ex. #	ester	product	yield
374			>99% $[MH]^+ = 402/404$
375			97% $[MH]^+ = 419$

Preparative Example 376



[0484] Step A

A mixture of NaOMe (5.40 g), thiourea (5.35 g) and commercially available 2-fluoro-3-oxo-butyric acid ethyl ester (6.27 mL) in anhydrous MeOH (50 mL) was stirred at 100°C

(temperature of the oil bath) for 5½ h and then allowed to cool to room temperature. The obtained beige suspension was concentrated and diluted with H_2O (50 mL). To the resulting aqueous solution was added concentrated HCl (9 mL). The formed precipitate was collected by filtration and washed with H_2O (100 mL) to afford the title compound as a pale beige solid (5.6 g, 70%). $[MH]^+ = 161$.

[0485] Step B

A suspension of the title compound from Step A above (5.6 g) and Raney®-nickel (50% slurry in H_2O, 8 mL) in H_2O (84 mL) was heated to reflux for 16 h. The mixture was allowed to cool to room temperature and then filtered. The filter cake was washed successively with MeOH and EtOAc and the combined filtrates were concentrated. The obtained viscous oily residue was diluted with EtOAc and concentrated to afford the title compound as a reddish solid (3.6 g, 80%). $[MH]^+ = 129$.

[0486] Step C

A mixture of the title compound from Step B above (3.6 g), K_2CO_3 (11.6 g) and $POBr_3$ (24.0 g) in anhydrous CH_3CN (200 mL) was heated to reflux for 19 h, cooled to room temperature and concentrated. A mixture of ice (180 g) and H_2O (30 mL) was added and the mixture was stirred for 30 min. The aqueous mixture was extracted with $CHCl_3$ (2 x 150 mL) and EtOAc (2 x 150 mL) and the combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated to afford the title compound as a yellow liquid (3.15 g, 58%). $[MH]^+ = 191/193$.

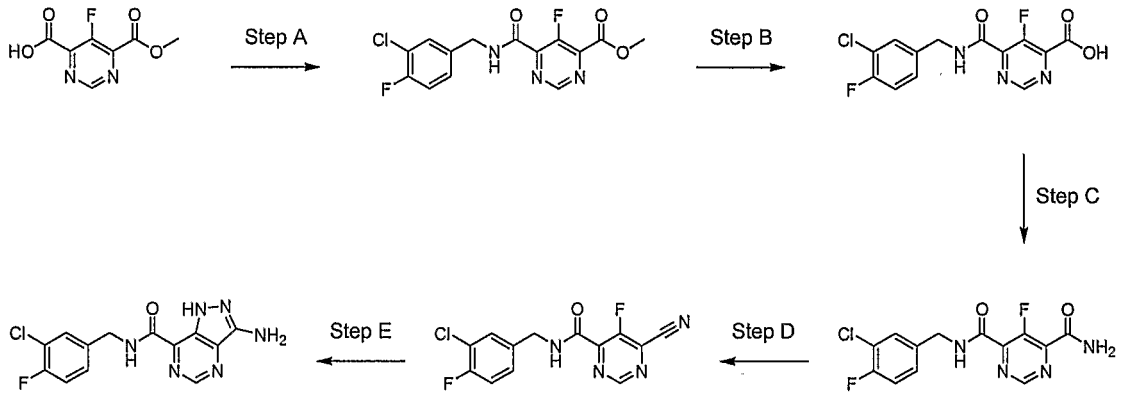
[0487] Step D

Under a carbon monoxide atmosphere (7 bar) a mixture of the title compound from Step C above (2.91 g), $Pd(OAc)_2$ (142 mg), 1,1'-bis-(diphenylphosphino)ferrocene (284 mg) and Et_3N (4.2 mL) in anhydrous DMA/MeOH (1:1, 150 mL) was heated at 80°C for 17 h. The mixture was cooled to room temperature, concentrated, absorbed on silica (500 mg) and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound as a beige solid (1.53 g, 59%). $[MH]^+ = 171$.

[0488] Step E

The title compound from Step D above (473 mg) was treated similarly as described in the Preparative Example 255, Step A to afford the title compound (514 mg, 92%). $[MH]^+ = 201$.

Preparative Example 377



[0489] Step A

The title compound from the Preparative Example 376, Step E (360 mg) was treated similarly as described in the Preparative Example 279, Step A, except using commercially available 3-chloro-4-fluoro-benzylamine instead of the title compound from the Preparative Example 214, Step A to afford the title compound (195 mg, 32%). $[MH]^+ = 342$.

[0490] Step B

The title compound from Step A above (195 mg) was treated similarly as described in the Preparative Example 331, Step A to afford the title compound (175 mg, 93%). $[MH]^+ = 328$.

[0491] Step C

The title compound from Step B above (175 mg) was treated similarly as described in the Preparative Example 280, Step A, except using a commercially available 0.5M solution of NH_3 in 1,4-dioxane instead of the title compound from the Preparative Example 138 to afford the title compound (160 mg, 92%). $[MH]^+ = 327$.

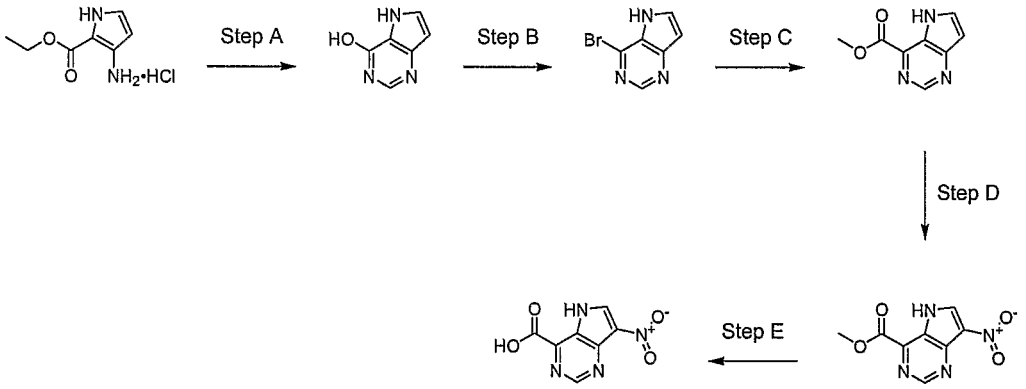
[0492] Step D

A 2M solution of oxalyl chloride in CH_2Cl_2 (450 μL) was diluted in DMF (8 mL) and then cooled to 0°C. Pyridine (144 μL) and a solution of the title compound from Step C above (146 mg) in DMF (2 mL) were added and the mixture was stirred at 0°C for 3 h and then at room temperature overnight. The mixture was concentrated, diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated to afford the title compound (57 mg, 41%). $[MH]^+ = 309$.

[0493] Step E

To a stirring solution of the title compound from Step D above (9 mg) in 1,4-dioxane (3 mL) was added a 1M solution of hydrazine hydrate in 1,4-dioxane (45 μL). The mixture was stirred at room temperature for 3 h and then concentrated to afford the title compound (10 mg, >99%). $[MH]^+ = 321$.

Preparative Example 378



[0494] Step A

A suspension of commercially available 3-amino-1*H*-pyrrole-2-carboxylic acid ethyl ester hydrochloride (5.06 g) and formamidine acetate (4.20 g) in EtOH (35 mL) was heated to reflux overnight and cooled to room temperature. The formed precipitate was collected by filtration, washed with EtOH and dried to afford the title compound as colorless needles (3.65 g, >99%). $[MH]^+ = 136$.

[0495] Step B

A mixture of the title compound from Step A above (491 mg) and $POBr_3$ (4 g) was heated to 80°C for 2 h. The mixture was cooled to room temperature, poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic extracts were concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as an off-white solid (276 mg, 38%). $[MH]^+ = 198/200$.

[0496] Step C

Under a carbon monoxide atmosphere (7 bar) a mixture of the title compound from Step B above (276 mg), $Pd(OAc)_2$ (13 mg), 1,1'-bis-(diphenylphosphino)ferrocene (31 mg) and Et_3N (370 μL) in anhydrous DMA/MeOH (1:2, 15 mL) was heated at 80°C for 3 d. The mixture was cooled to room temperature, concentrated, absorbed on silica and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a brown solid (260 mg, >99%). $[MH]^+ = 178$.

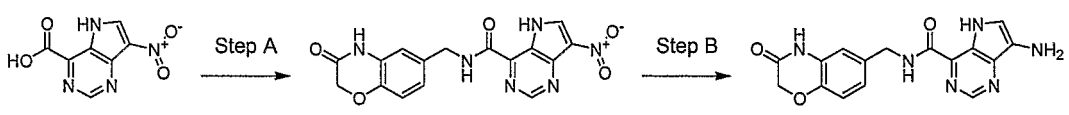
[0497] Step D

To the ice cooled title compound from Step C above (120 mg) was added concentrated HNO_3 ($\rho = 1.5$, 1 mL). The mixture was stirred at 0°C (ice bath) for 30 min, the cooling bath was removed and stirring was continued for 30 min. Ice was added and the formed precipitate was collected by filtration and dried to afford the title compound as a brown solid (87 mg, 58%). $[MH]^+ = 223$.

[0498] Step E

To the title compound from Step D above (87 mg) was added a solution of LiOH (47 mg) in H_2O. The resulting mixture was stirred for 2 h and then acidified with 1N aqueous HCl. The formed precipitate was collected by filtration and dried to afford the title compound as a brown solid (93 mg, >99%). $[MH]^+ = 209$.

Preparative Example 379



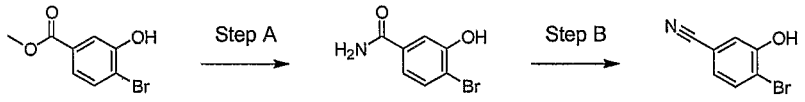
[0499] Step A

To a solution of the title compound from the Preparative 378, Step E above (93 mg) and the title compound from the Preparative Example 161 (110 mg) in DMF (5 mL) were added *N*-methylmorpholine (40 μL), EDCI (120 mg) and HOAt (60 mg). The mixture was stirred overnight and then concentrated. 10% aqueous citric acid was added and the formed precipitate was collected by filtration and dried to afford the title compound as a brown solid (91.5 mg, 63%). $[MH]^+ = 369$.

[0500] Step B

A mixture of the title compound from Step A above (91 mg), AcOH (200 μL) and Pd/C (10wt%, 55 mg) in THF/MeOH was hydrogenated at atmospheric pressure overnight, filtered, concentrated and diluted with saturated aqueous $NaHCO_3$. The formed precipitate was collected by filtration and purified by preparative thin layer chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a brown solid (12 mg, 9%). $[MH]^+ = 339$.

Preparative Example 380



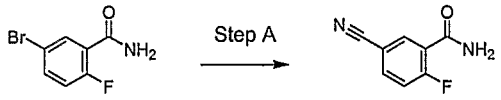
[0501] Step A

Commercially available 4-bromo-3-hydroxy-benzoic acid methyl ester (500 mg) was treated similarly as described in the Preparative Example 32, Step A to afford the title compound (475 mg, >99%). $[MH]^+ = 216$.

[0502] Step B

The title compound from Step A above (475 mg) was treated similarly as described in the Preparative Example 32, Step B to afford the title compound as a colorless solid (316 mg, 73%). $[MH]^+ = 298$.

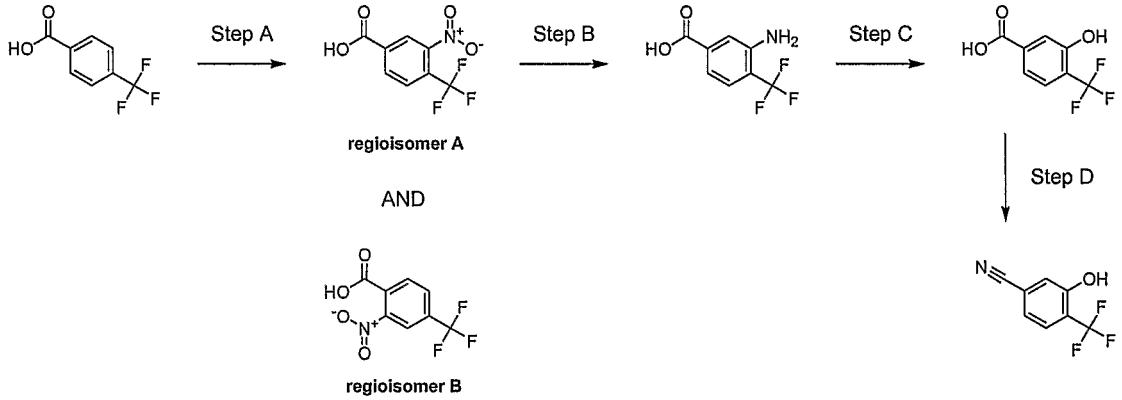
Preparative Example 381



[0503] Step A

Commercially available 5-bromo-2-fluoro-benzamide (500 mg) was treated similarly as described in the Preparative Example 25, Step A to afford the title compound as colorless needles (196 mg, 52%). $[MH]^+ = 165$.

Preparative Example 382



[0504] Step A

At room temperature commercially available 4-trifluoromethyl benzoic acid (4.90 g) was slowly added to a 90% solution of HNO_3 (10 mL). H_2SO_4 (12 mL) was added and the mixture was stirred at room temperature for 20 h. The mixture was poured on a mixture of ice (250 g) and H_2O (50 mL). After 30 min the precipitate was collected by filtration, washed with H_2O and air dried. Purification by chromatography (CH_2Cl_2/cyclohexane/AcOH) afforded the title compound as regioisomer A (2.30 g, 38%) and regioisomer B (1.44 g, 23%). ^{1}H-NMR (acetone-d_6) regioisomer A: □= 8.36 (s, 1 H), 8.13-8.25 (m, 2 H), regioisomer B: □= 8.58 (s, 1 H), 8.50 (m, 1 H), 8.20 (d, 1 H).

[0505] Step B

A mixture of the regioisomer A from Step A above (1.44 g) and Pd/C (10wt%, 400 mg) in MeOH (150 mL) was hydrogenated at atmospheric pressure for 1 h and filtered.

The filter cake was washed with MeOH (50 mL) and the combined filtrates were concentrated to afford the title compound (1.20 g, 95%). $[MH]^+ = 206$.

[0506] Step C

To a cooled to (0-5°C) mixture of the title compound from Step B above (1.2 g) and concentrated H_2SO_4 (6 mL) in H_2O (34 mL) was slowly added a solution of $NaNO_3$ (420 mg) in H_2O (6 mL). The mixture was stirred at 0-5°C for 45 min and then added to a mixture of H_2O (48 mL) and concentrated H_2SO_4 (6 mL), which was kept at 135°C (temperature of the oil bath). The resulting mixture was stirred at 135°C (temperature of the oil bath) for 2½ h, cooled to room temperature, diluted with ice water (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with saturated aqueous NaCl (50 mL), dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/cyclohexane/AcOH) to afford the title compound (797 mg, 66%). $[MH]^+ = 207$.

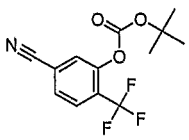
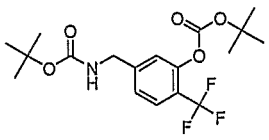
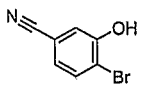
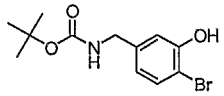
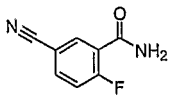
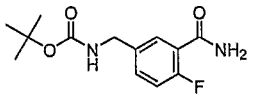
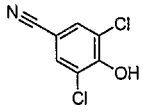
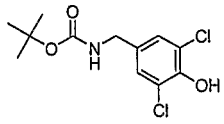
[0507] Step D

To a cooled (–30°C) solution of the title compound from Step C above (790 mg) and NEt_3 (1.4 mL) in THF (45 mL) was added ethyl chloroformate (790 μL). The mixture was stirred at –30°C to –20°C for 1 h and then filtered. The precipitated salts were washed with THF (20 mL). The combined filtrates were cooled to –20°C and a 33% solution of NH_3 in H_2O (20 mL) was added. The mixture was stirred at –20°C for 20 min, then the cooling bath was removed and the mixture was stirred at room temperature for 40 min. Then the mixture was concentrated and dissolved in THF (25 mL) and CH_3CN (6 mL). Pyridine (3.15 mL) was added and the mixture was cooled to 0°C. Trifluoroacetic anhydride (2.73 mL) was added and the mixture was stirred at 0°C for 3 h. Then the mixture was concentrated in vacuo, diluted with MeOH (22 mL) and 10% aqueous K_2CO_3 (22 mL) and stirred at room temperature for 48 h. The mixture was concentrated to ~20 mL, acidified (pH ~1) with 1N aqueous HCl and extracted with EtOAc (2 x 100 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (490 mg, 67%). $[MH]^+ = 188$.

Preparative Examples 383-386

[0508] Following a similar procedure as described in the Preparative Example 34, except using the nitriles indicated in Table I-17 below, the following compounds were prepared.

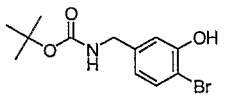
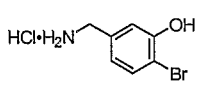
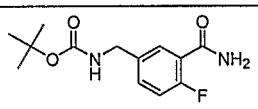
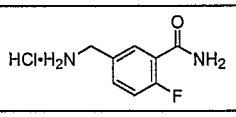
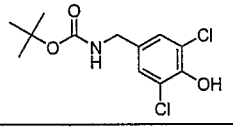
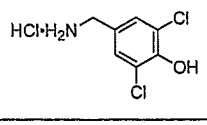
Table I-17

Prep. Ex. #	nitrile	product	yield
383			51% ^{1}H-NMR (DMSO-d_6) □= 7.78 (d, 1 H), 7.58 (t, 1 H), 7.38 (d, 1 H), 7.32 (s, 1 H), 4.25 (d, 2 H), 1.52 (s, 9 H), 1.40 (s, 9 H)
384			53% $[MNa]^+ = 324/326$
385			n.d. $[MNa]^+ = 291$
386			n.d. $[MH]^+ = 292$

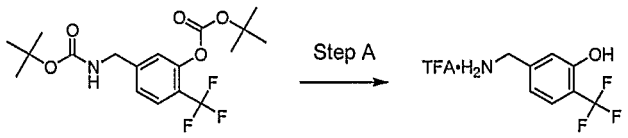
Preparative Examples 387–389

[0509] Following a similar procedure as described in the Preparative Example 133, except using the protected amines indicated in Table I-18 below, the following compounds were prepared.

Table I-18

Prep. Ex. #	protected amine	product	yield
387			>99% $[M\text{-}Cl]^+ = 201/203$
388			n.d. $[M\text{-}Cl]^+ = 169$
389			>99% $[M\text{-}Cl]^+ = 192$

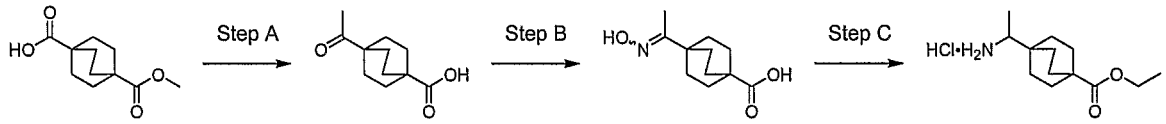
Preparative Example 390



[0510] Step A

The title compound from the Preparative Example 383 (42 mg) was treated similarly as described in the Preparative Example 208, Step A to afford the title compound (32 mg, 98%). $[M\text{-}TFA]^+ = 165$.

Preparative Example 391



[0511] Step A

A solution of title compound from the Preparative Example 39, Step C (1.0 g) in $SOCl_2$ (5 mL) was heated to reflux for 3 h, concentrated and coevaporated several times with cyclohexane to afford the corresponding acid chloride. A mixture of magnesium turnings (127 mg) and EtOH (100 μL) in dry benzene (2 mL) was heated to reflux until the dissolution of the magnesium started. A mixture of diethyl malonate (810 μl) and EtOH (700 μL) in benzene (3 mL) was added over a period of 30 min and heating to reflux was continued for 3 h (complete dissolution of the magnesium). The EtOH was then removed by azeotropic distillation with fresh portions of benzene and the volume was brought to ~ 5 mL by addition of benzene. The mixture was heated to reflux, a solution of the acid chloride in benzene (5 mL) was added over a period of 30 min and heating to reflux was continued for 3½ h. The resulting viscous mixture was poured on a mixture of ice and 6N aqueous HCl. The organic phase was separated and the aqueous phase was extracted was benzene (2 x 10 mL). The combined organic phases were washed with H_2O, dried ($MgSO_4$), filtered and concentrated. The remaining residue was diluted with AcOH (25 mL) and concentrated HCl (25 mL), heated to reflux for 16 h, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound (665 mg, 76%). $[MH]^+ = 197$.

[0512] Step B

A mixture of hydroxylamine hydrochloride (807 mg) and pyridine (4.5 mL) in EtOH (4.5 mL) was heated to reflux for 5 min, the title compound from Step A above (759 mg) was added and heating to reflux was continued for 3 h. The mixture was cooled, concentrated and diluted with cold 3N aqueous HCl (30 mL). The formed precipitate was collected by filtration, washed with H_2O and air dried to afford the title compound (590 mg, 72%). $[MH]^+ = 212$.

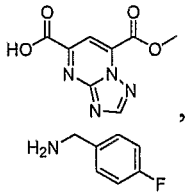
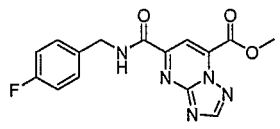
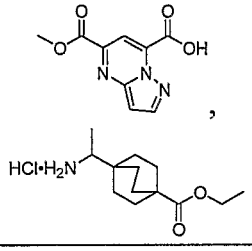
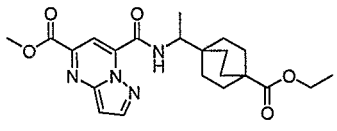
[0513] Step C

A mixture of the title compound from Step B above (440 mg), 6N aqueous HCl (5 mL) and PtO_2 (95 mg) in 90% aqueous EtOH (40 mL) was hydrogenated at atmospheric pressure for 36 h, filtered and concentrated to afford the crude title compound as a colorless solid (436 mg, 80%). $[M\text{-}Cl]^+ = 226$.

Preparative Examples 392-393

[0514] Following similar procedures as described in the Preparative Examples 280, except using the acids and amines indicated in Table I-19 below, the following compounds were prepared.

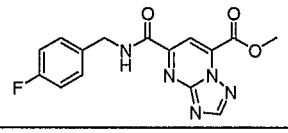
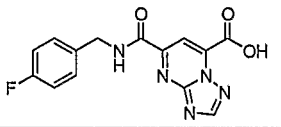
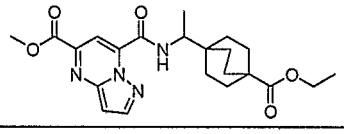
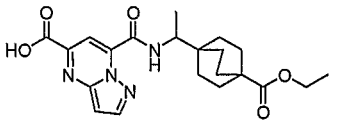
Table I-19

Prep. Ex. #	acid, amine	product	yield
392			69% $[MH]^+ = 330$
393			41% $[MH]^+ = 429$

Preparative Examples 394-395

[0515] Following similar procedures as described in the Preparative Examples 331, except using the esters indicated in Table I-20 below, the following compounds were prepared.

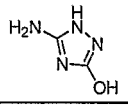
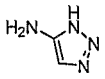
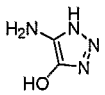
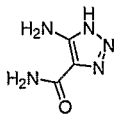
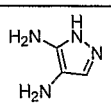
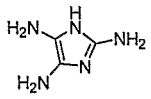
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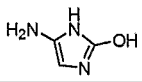
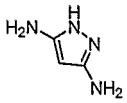
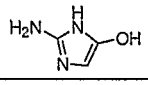
Prep. Ex. #	ester	product	yield
394			95% $[MH]^+ = 316$
395			95% $[MH]^+ = 415$

Preparative Examples 396-404

[0516] The following intermediates are known by literature as indicated in Table I-21 below.

Table I-21

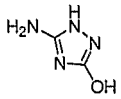
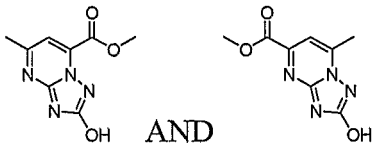
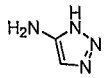
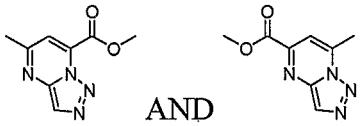
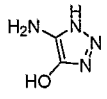
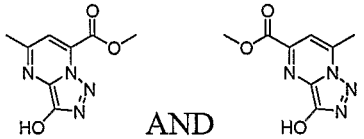
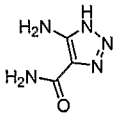
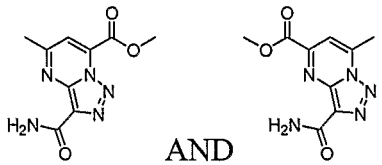
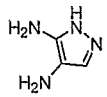
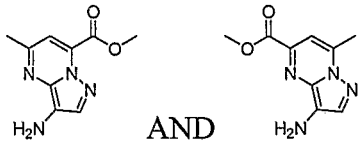
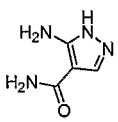
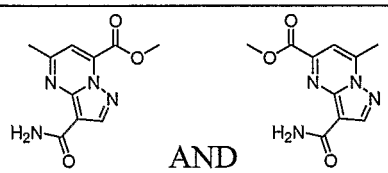
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397		J. Chem. Soc., 1971, 1501-1507
398		Annali di Chimica, 1967, 57, 680-687
399		J. Am. Chem. Soc., 78, 1956, 5832-5835
400		J. Chem. Soc. 1968, 2159-2168
401		Chem. Ber., 1976, 109, 1625-1637

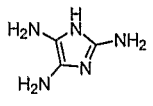
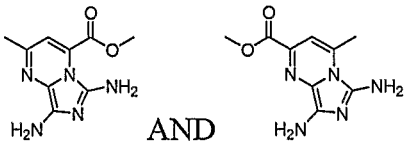
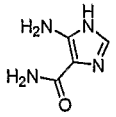
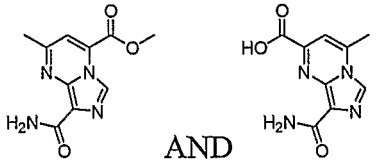
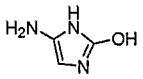
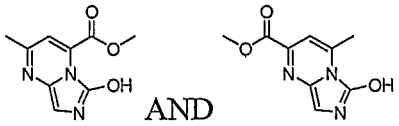
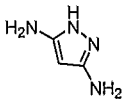
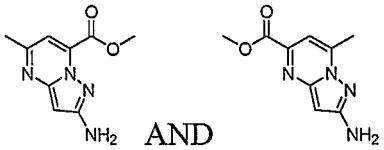
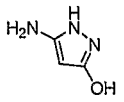
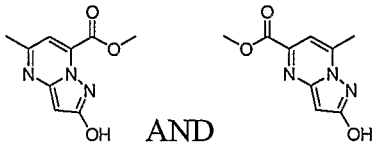
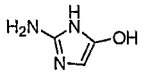
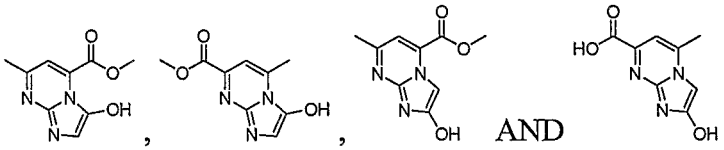
Prep. Ex. #	intermediate	reference
402		Patent: DE 3305778
403		J. Org. Chem., 33, 6, 1968, 2606
404		J. Med. Chem. 1991, 34, 1845-1849

Preparative Examples 405-415

[0517] If one were to follow a similar procedure as described in the Preparative Example 246, except using the amines indicated in Table I-22 Below, the following compounds would be obtained.

Table I-22

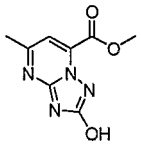
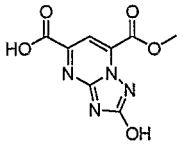
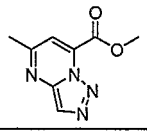
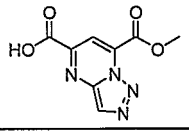
Prep. Ex. #	amine	product
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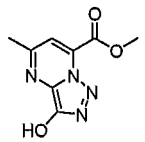
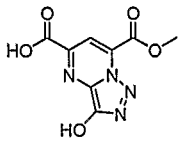
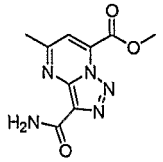
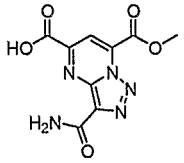
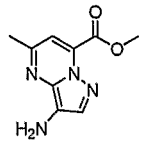
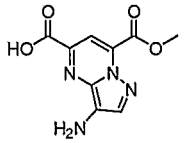
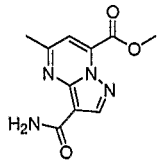
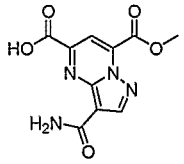
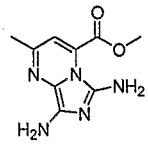
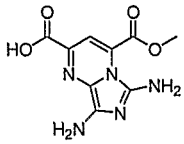
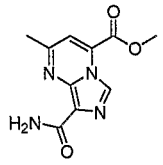
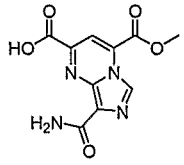
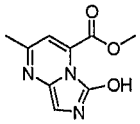
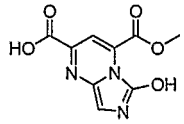
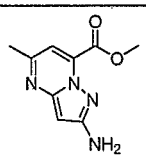
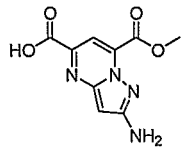
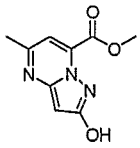
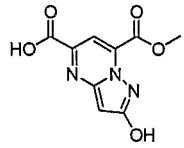
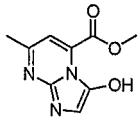
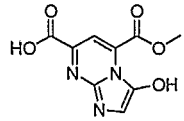
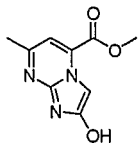
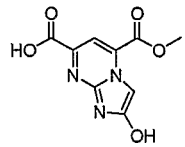
Prep. Ex. #	amine	product
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Preparative Examples 416-428

[0518] If one were to follow a similar procedure as described in the Preparative Example 255, except using the amines indicated in Table I-23 Below, the following compounds would be obtained.

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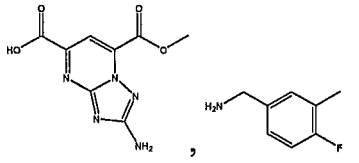
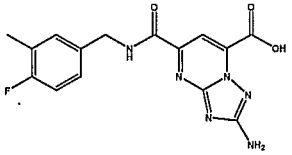
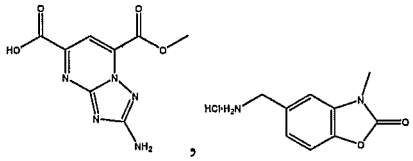
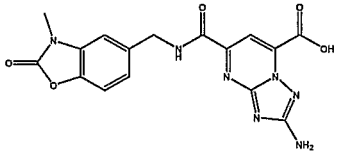
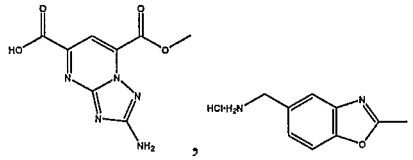
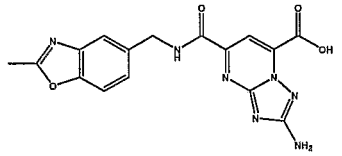
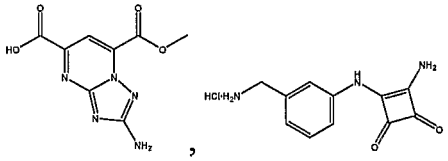
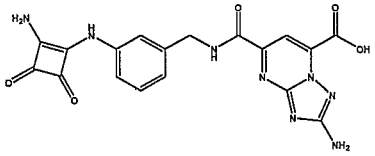
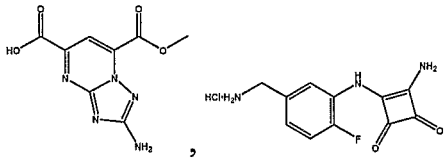
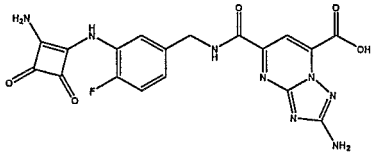
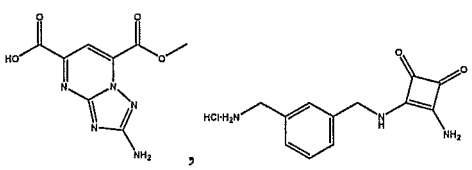
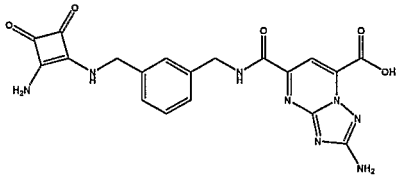
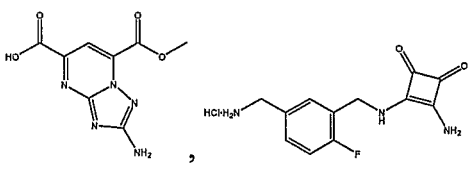
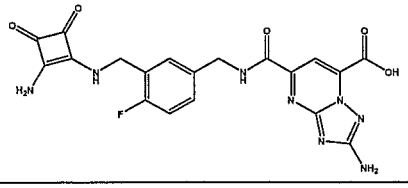
Prep. Ex. #	intermediate	product
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417		

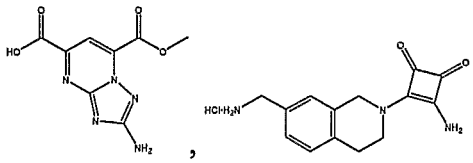
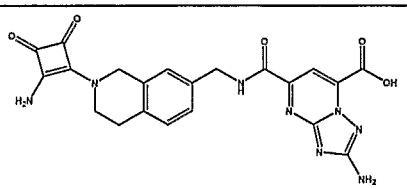
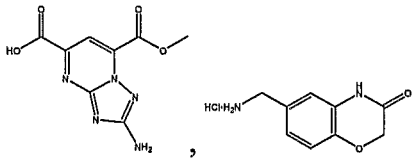
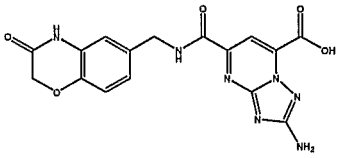
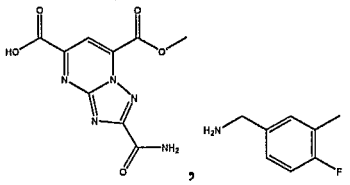
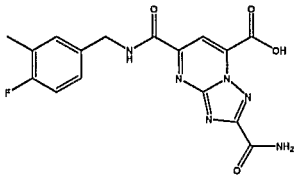
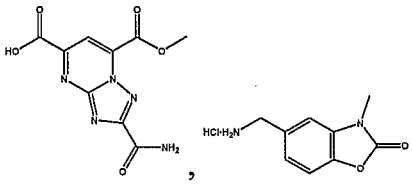
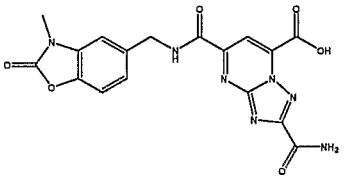
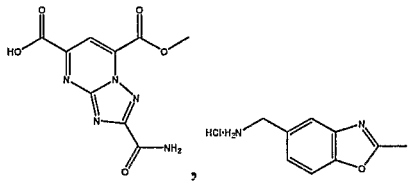
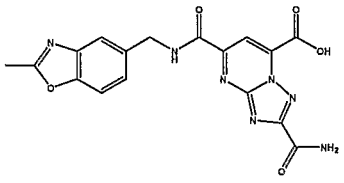
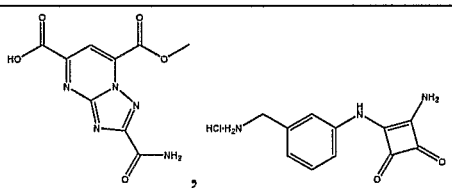
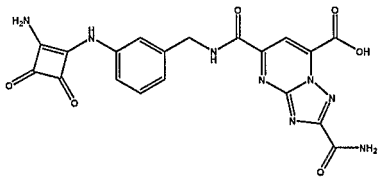
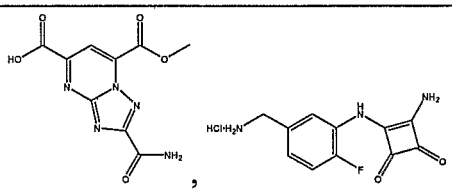
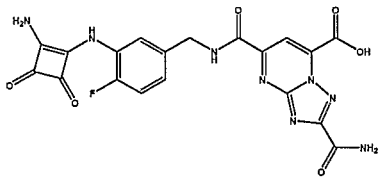
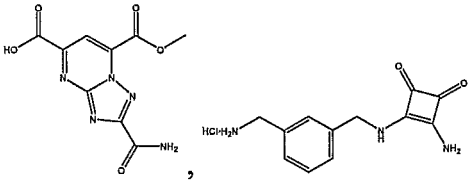
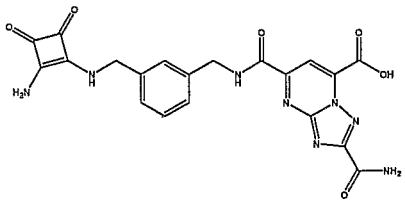
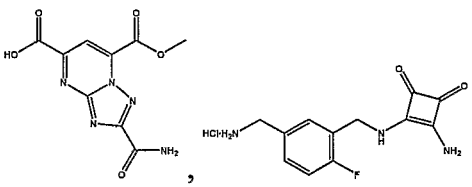
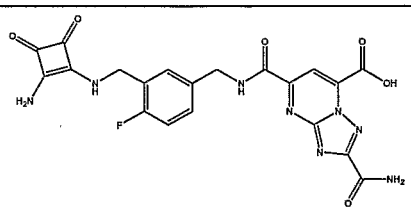
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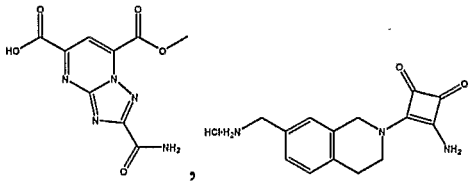
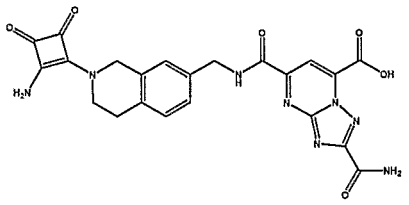
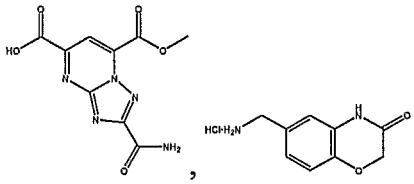
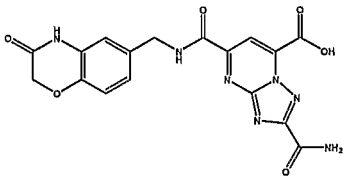
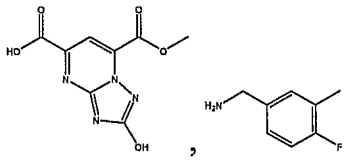
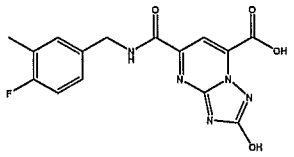
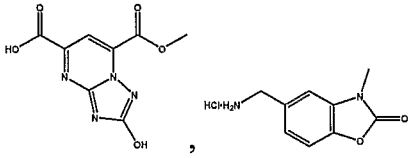
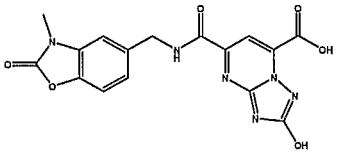
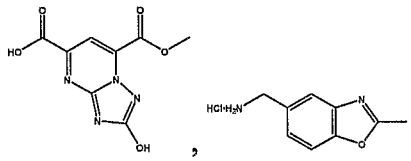
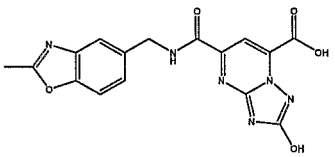
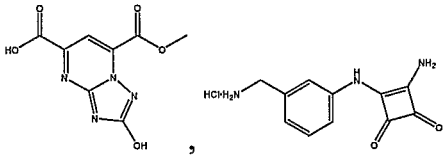
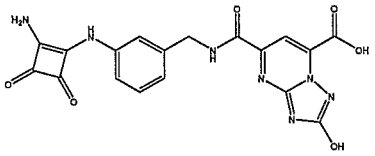
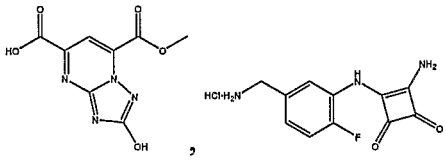
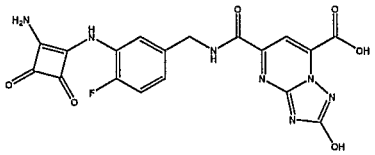
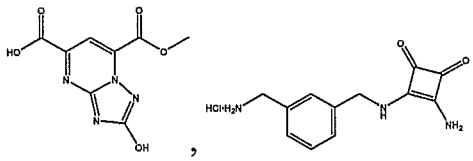
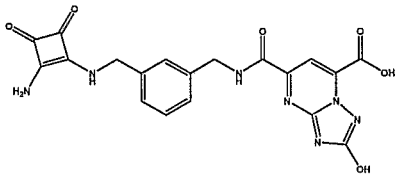
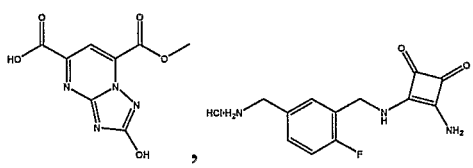
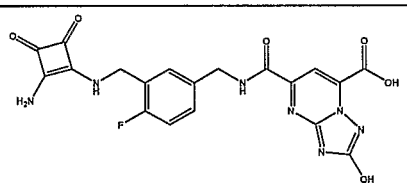
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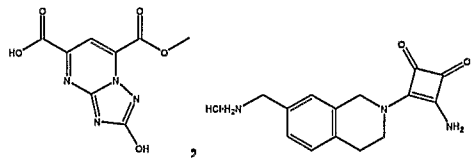
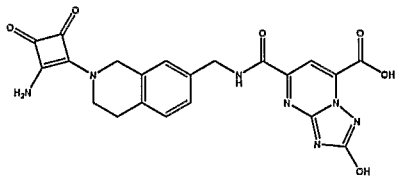
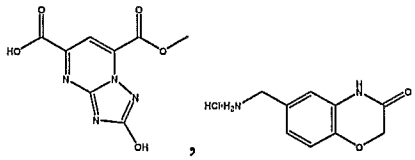
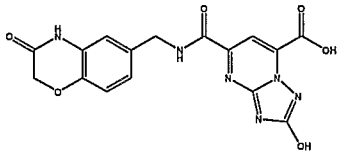
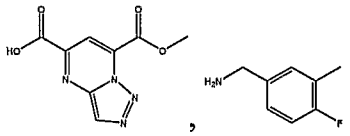
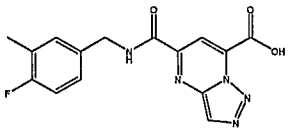
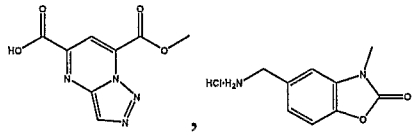
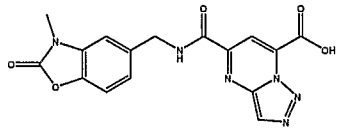
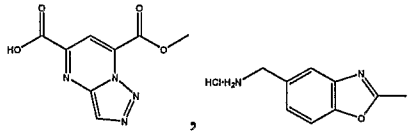
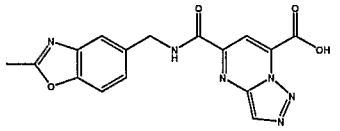
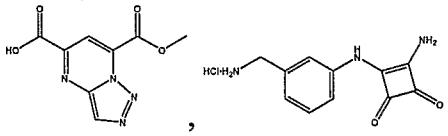
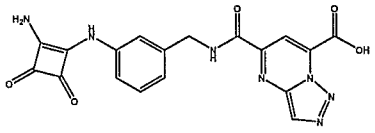
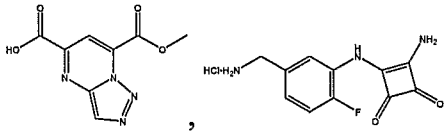
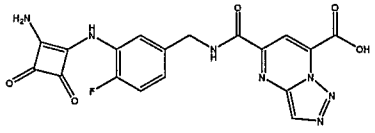
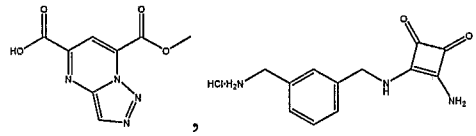
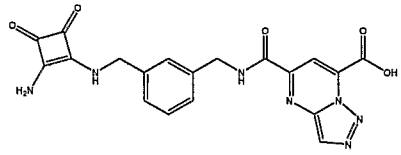
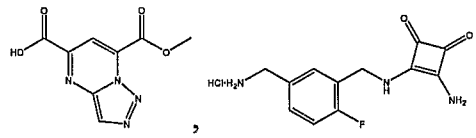
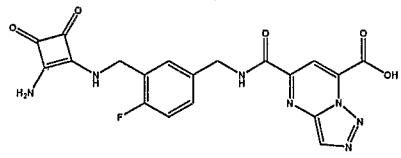
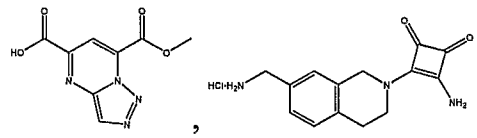
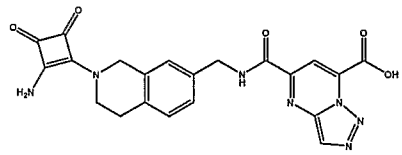
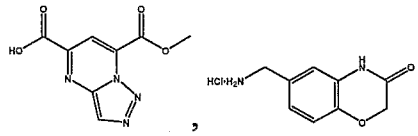
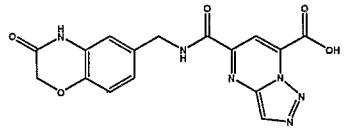
[0519] If one were to follow similar procedures as described in the Preparative Examples 279, 280, 281, 278 or 282, except using the acids and amines indicated in Table I-24 below, and if one were to treat the obtained esters similarly as described in the Preparative Examples 331, 332 or 333, the following compounds would be obtained.

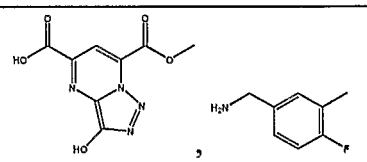
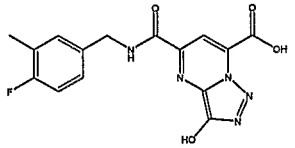
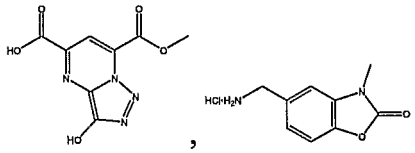
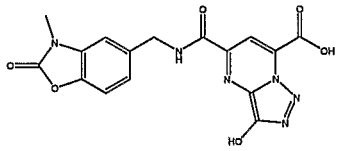
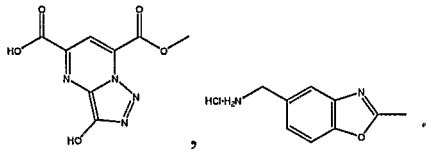
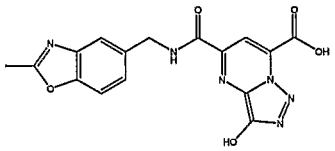
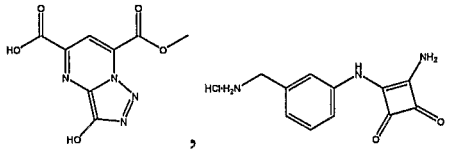
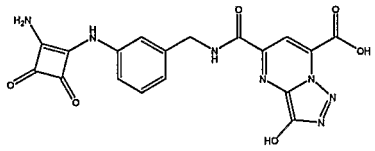
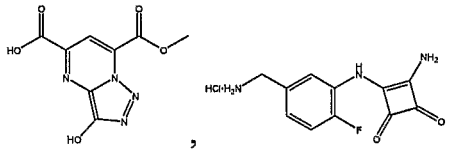
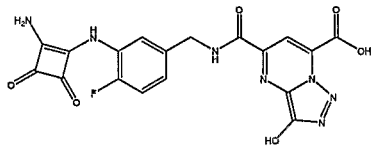
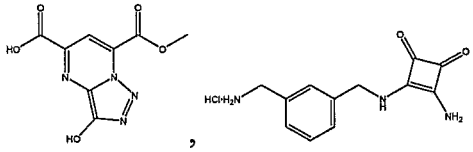
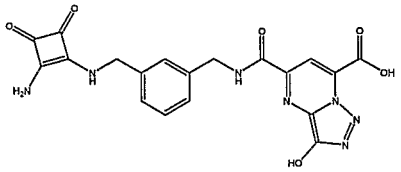
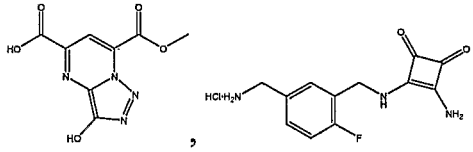
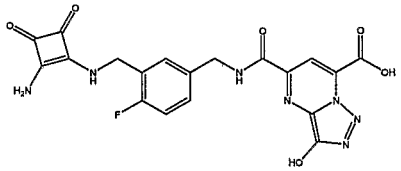
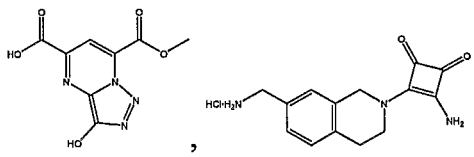
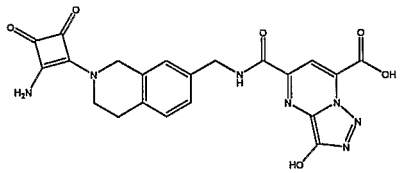
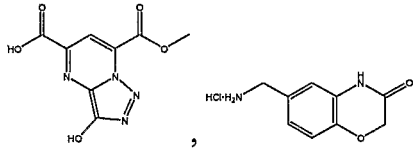
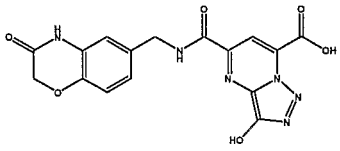
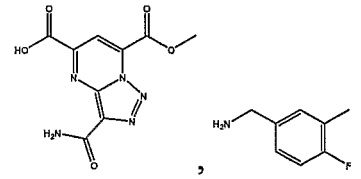
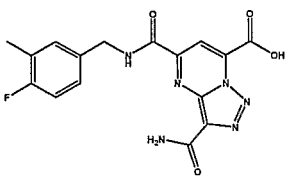
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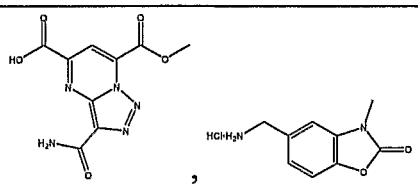
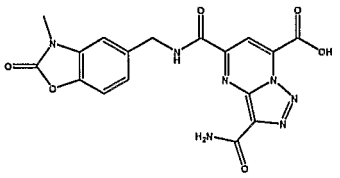
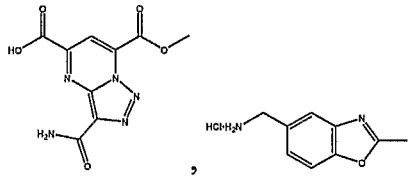
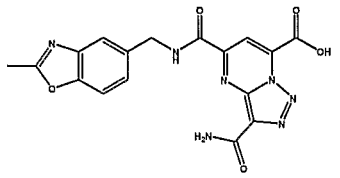
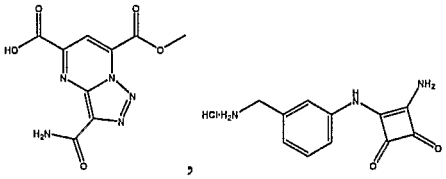
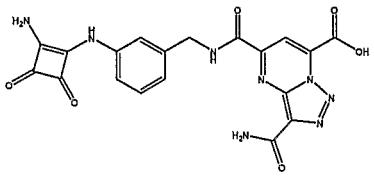
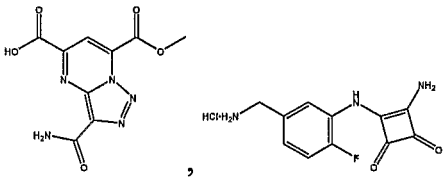
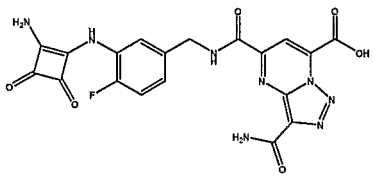
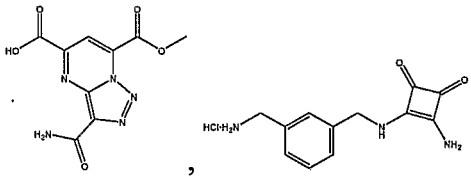
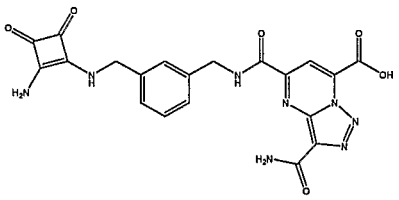
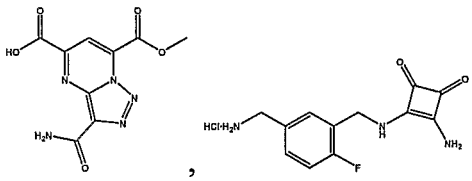
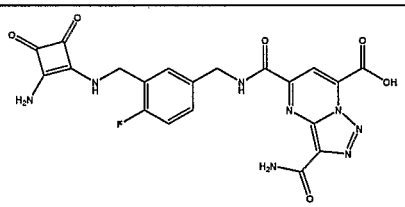
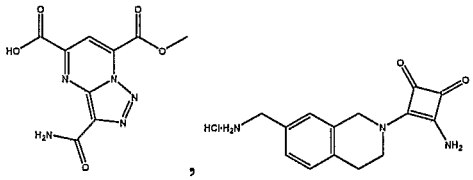
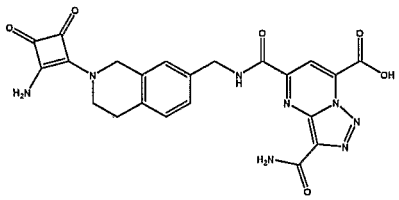
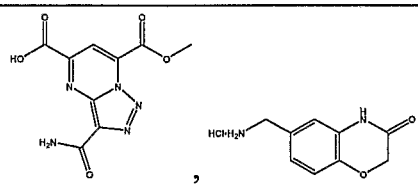
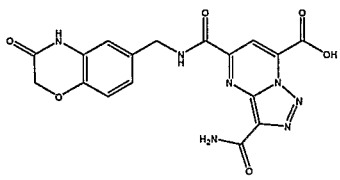
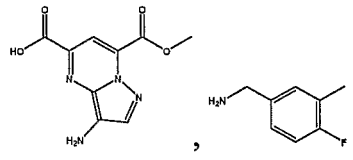
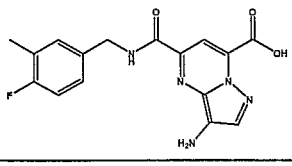
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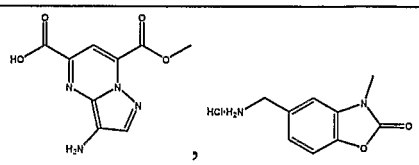
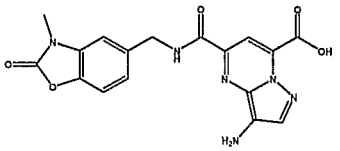
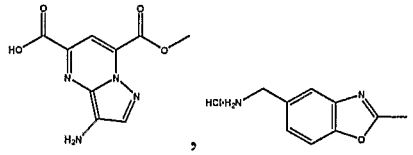
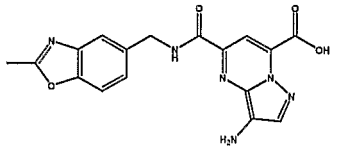
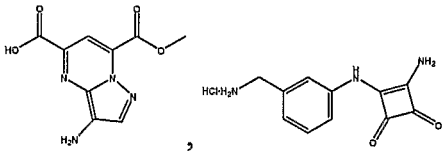
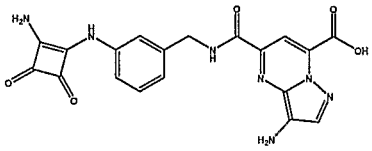
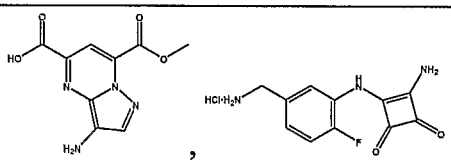
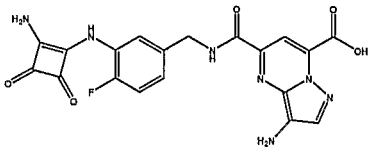
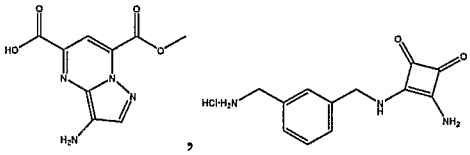
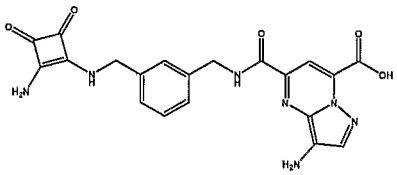
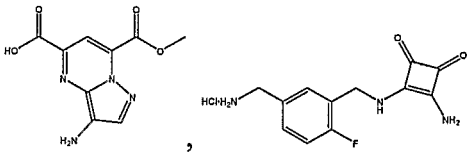
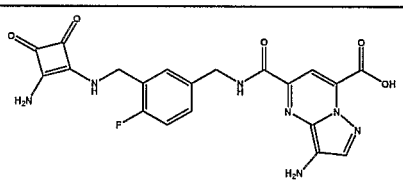
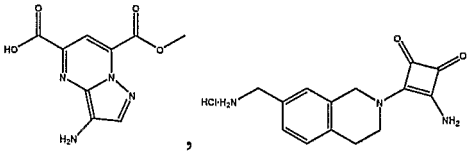
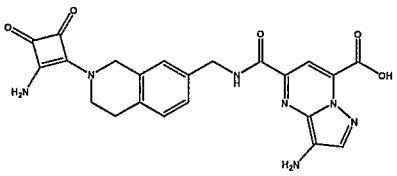
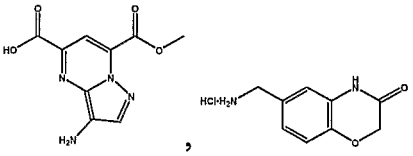
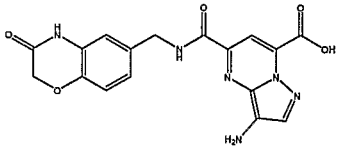
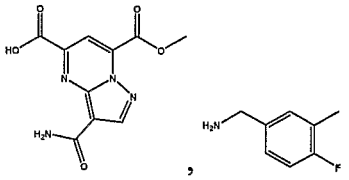
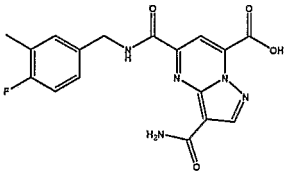
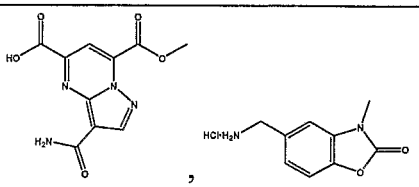
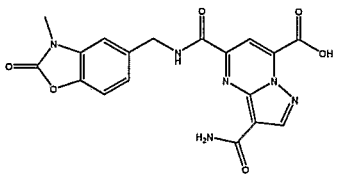
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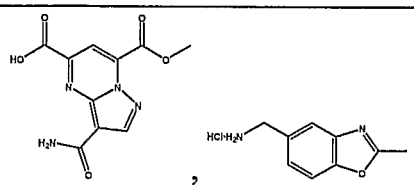
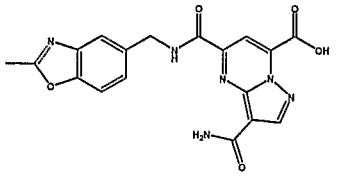
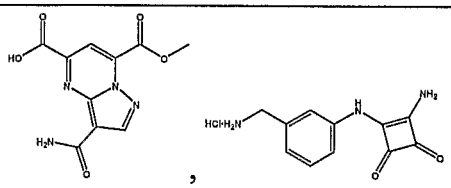
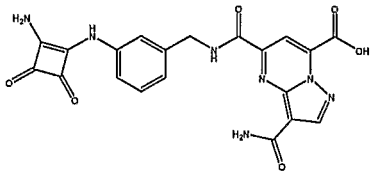
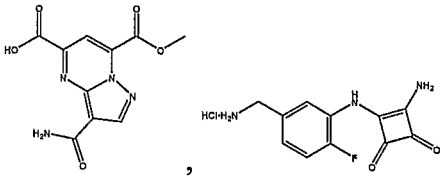
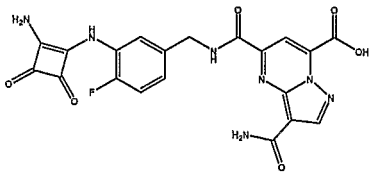
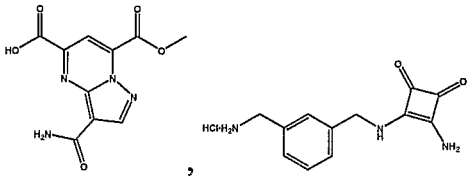
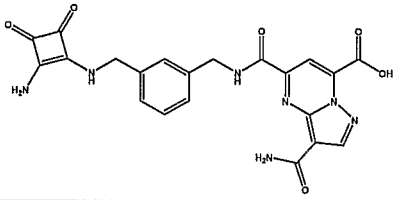
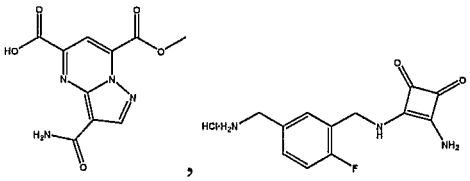
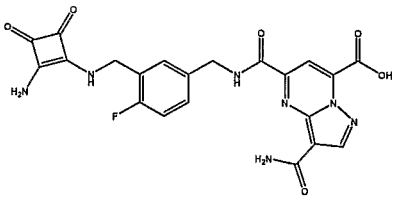
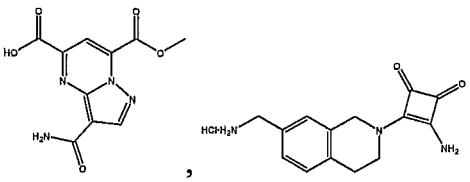
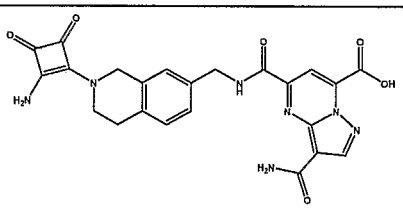
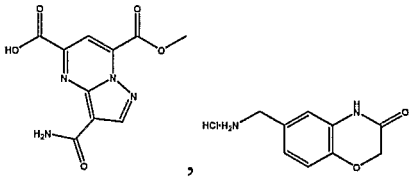
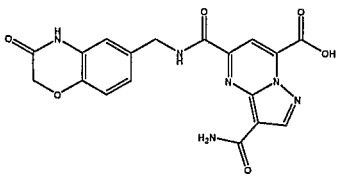
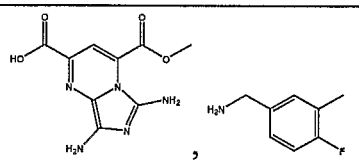
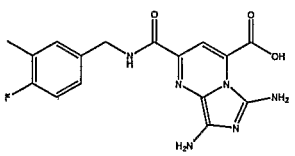
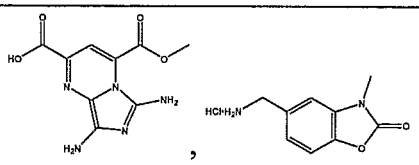
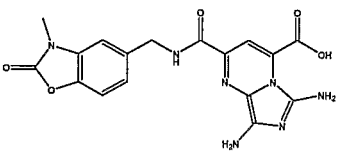
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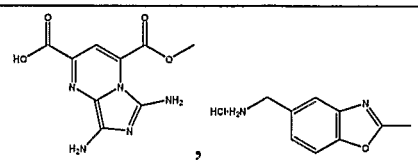
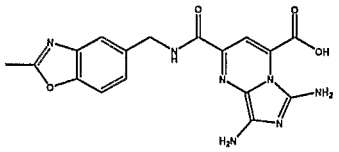
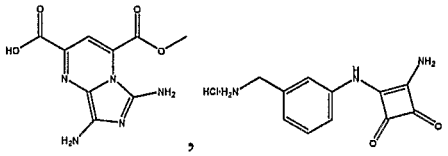
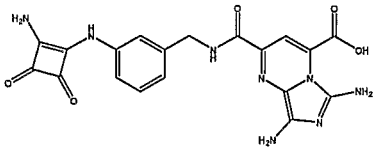
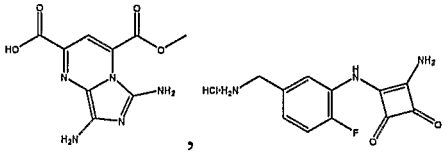
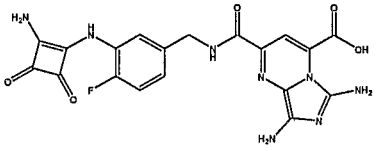
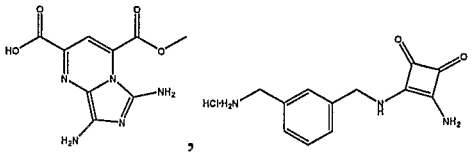
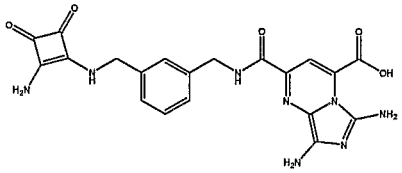
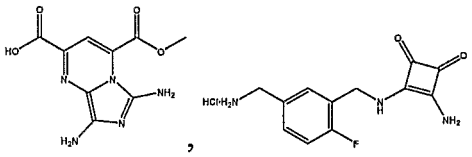
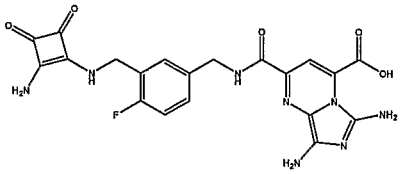
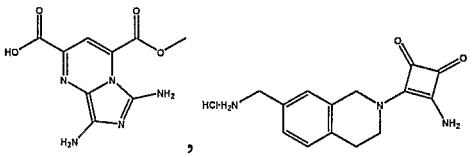
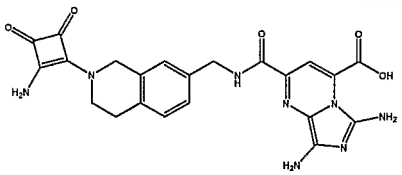
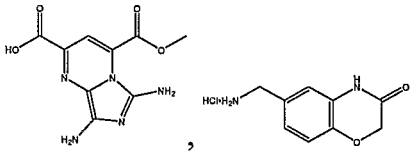
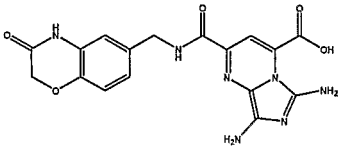
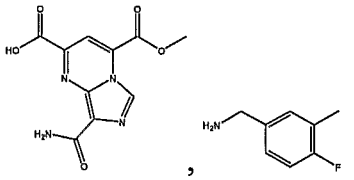
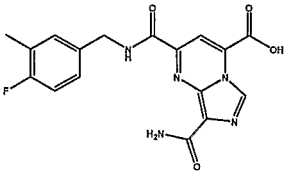
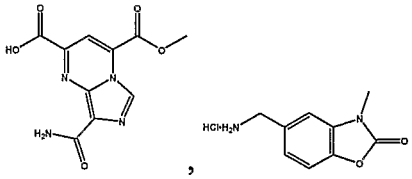
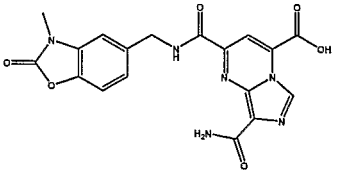
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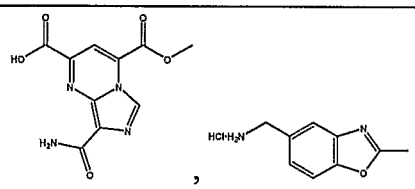
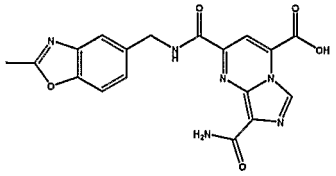
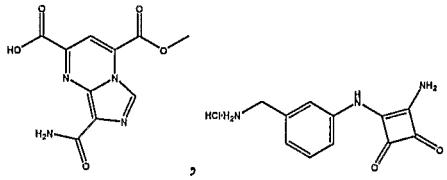
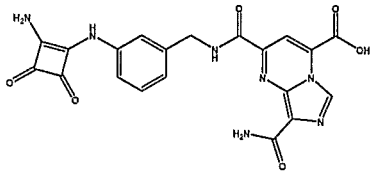
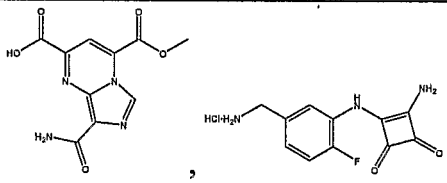
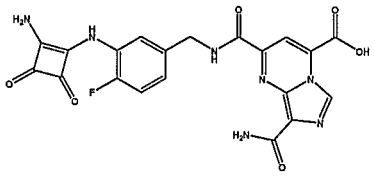
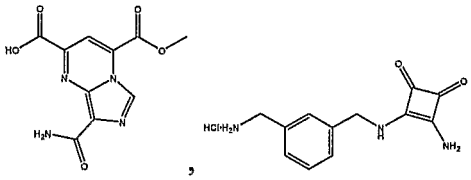
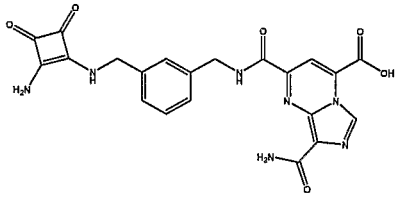
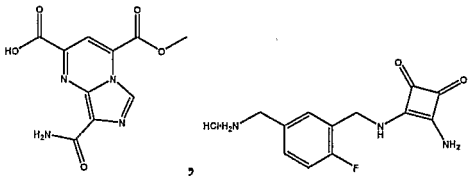
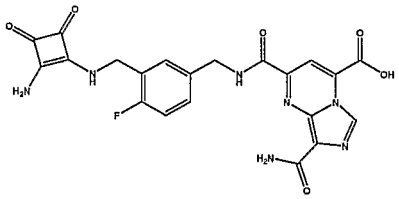
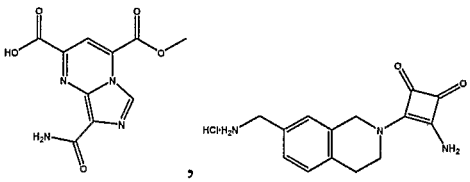
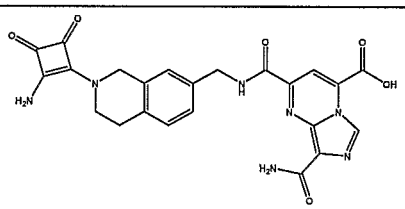
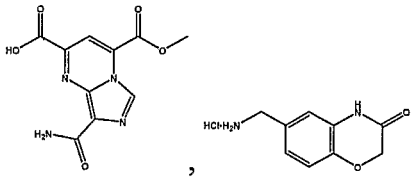
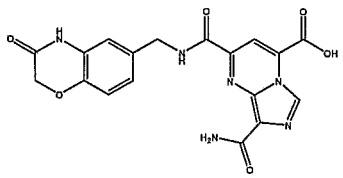
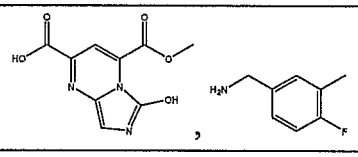
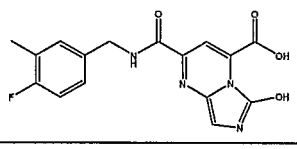
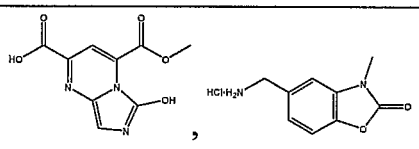
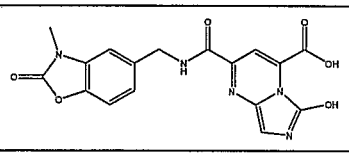
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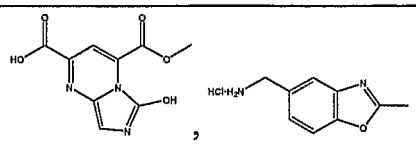
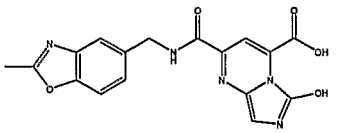
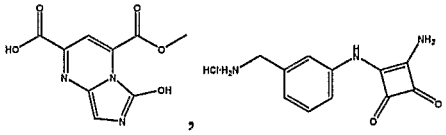
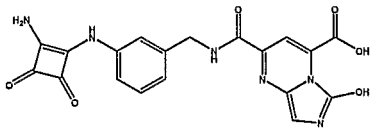
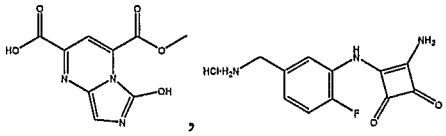
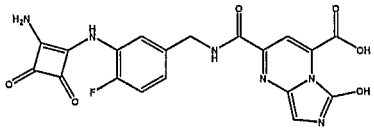
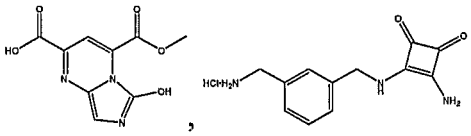
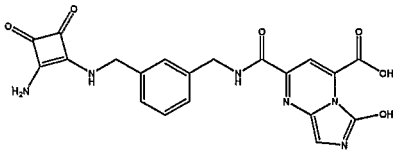
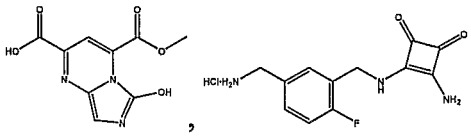
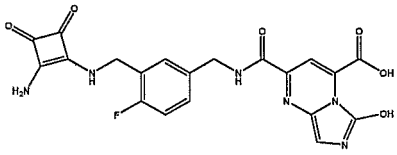
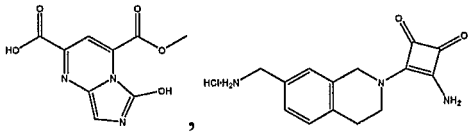
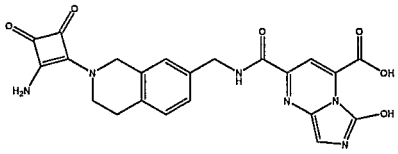
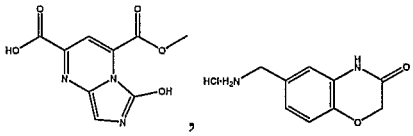
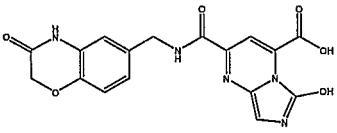
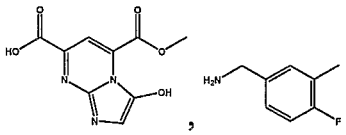
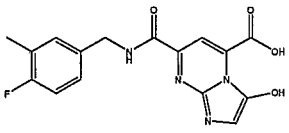
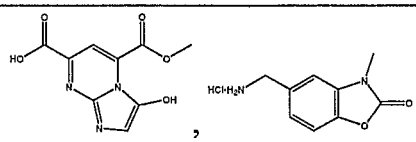
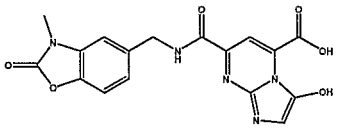
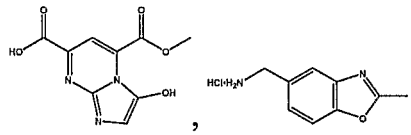
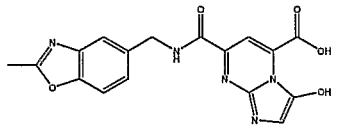
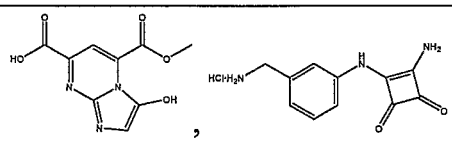
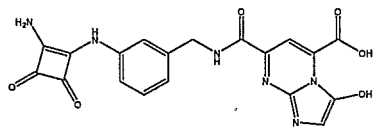
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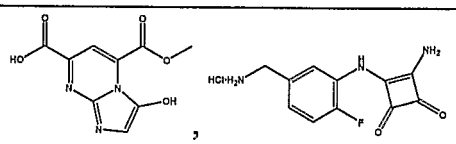
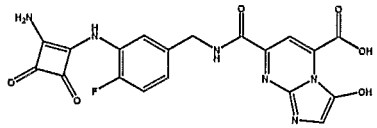
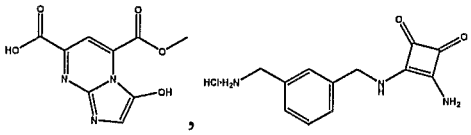
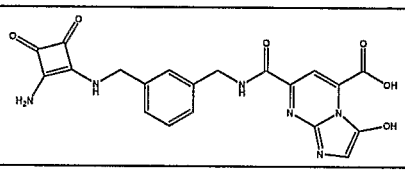
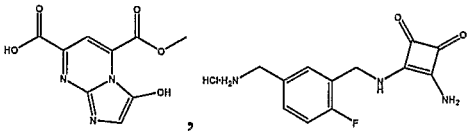
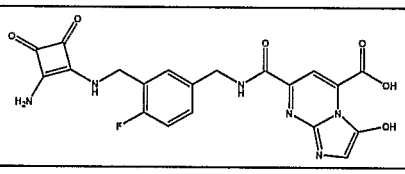
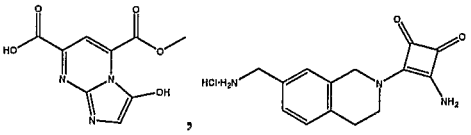
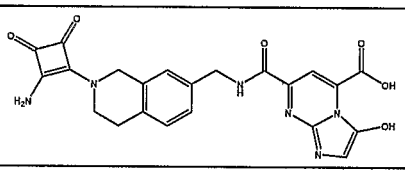
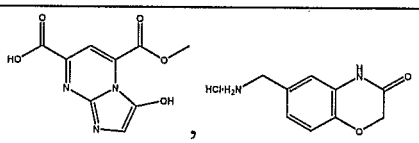
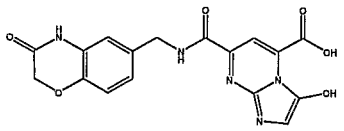
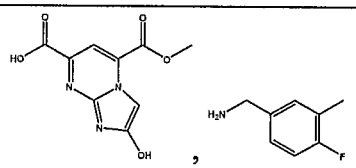
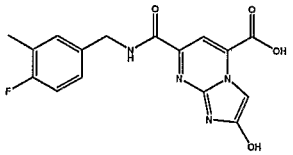
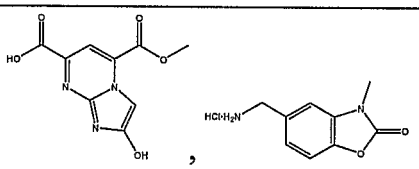
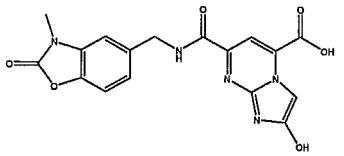
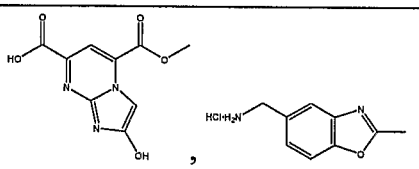
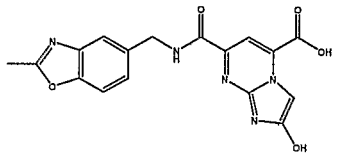
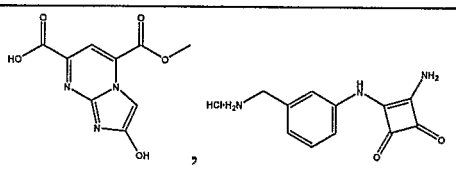
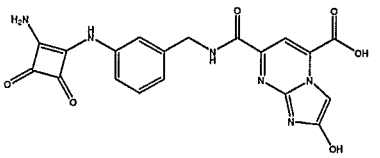
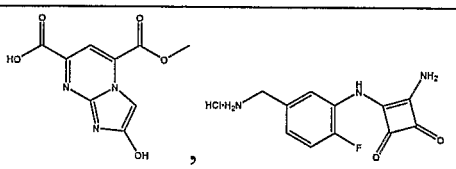
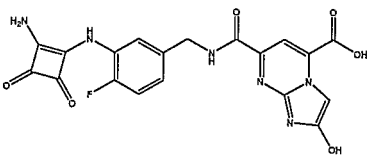
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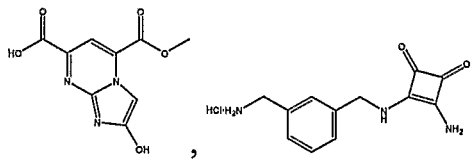
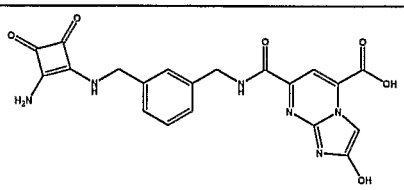
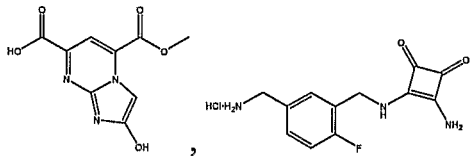
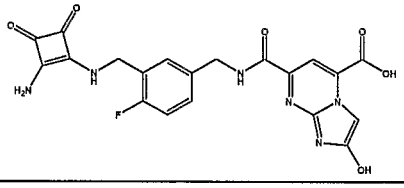
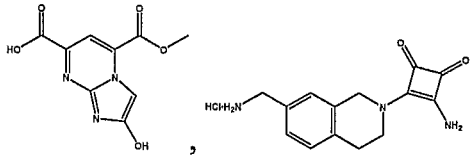
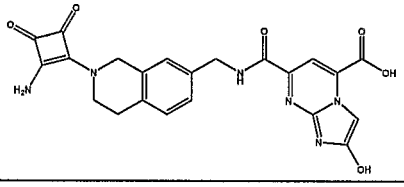
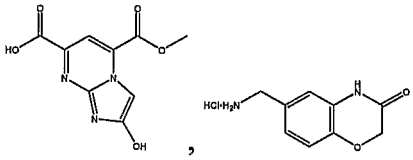
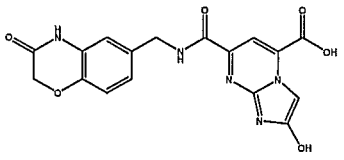
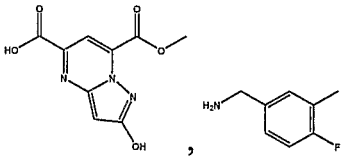
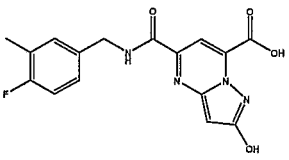
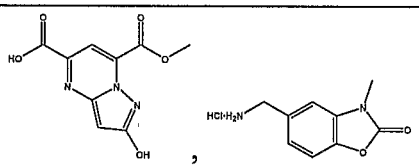
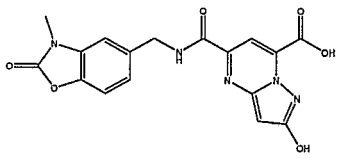
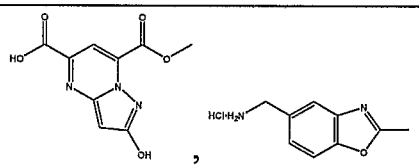
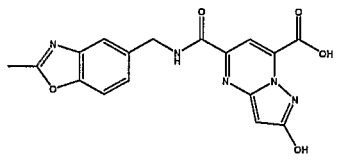
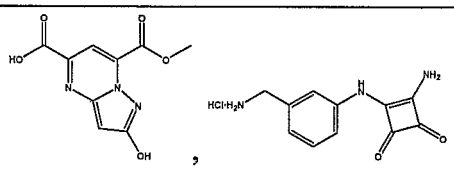
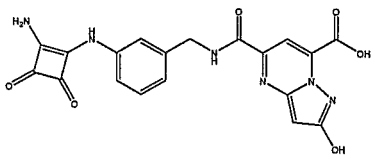
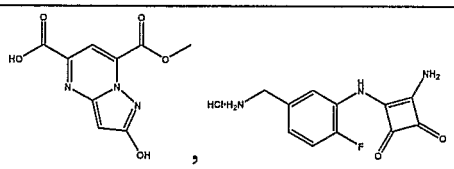
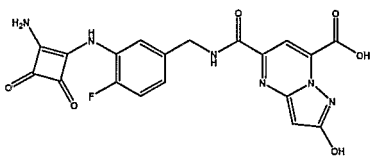
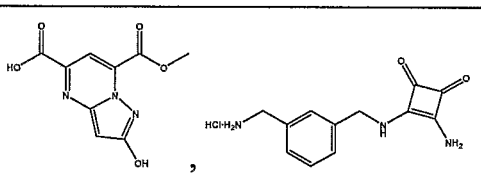
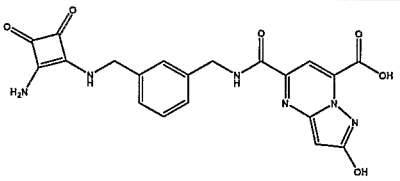
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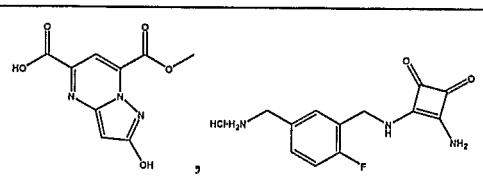
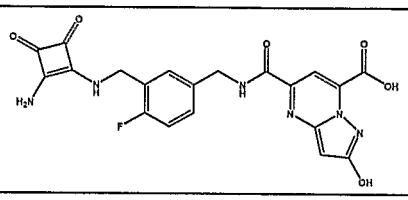
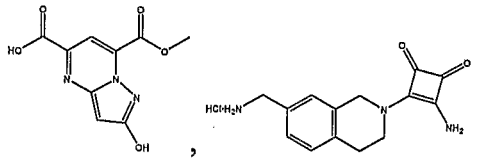
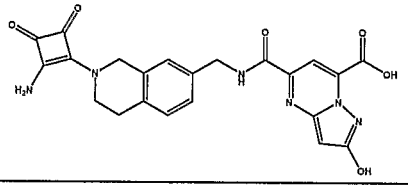
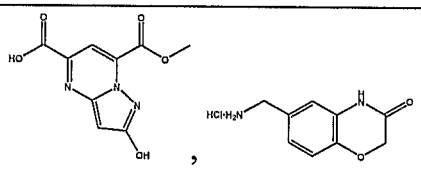
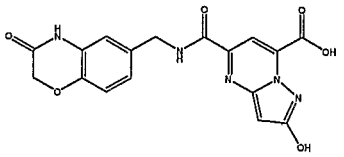
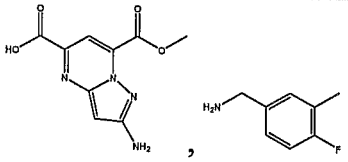
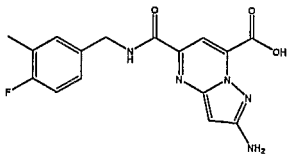
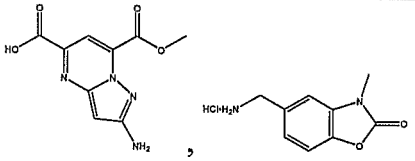
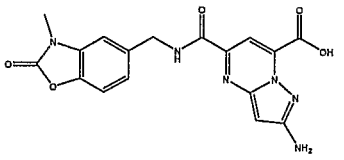
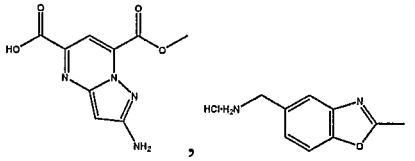
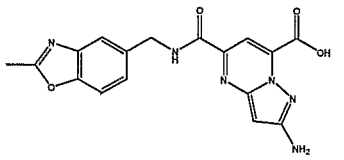
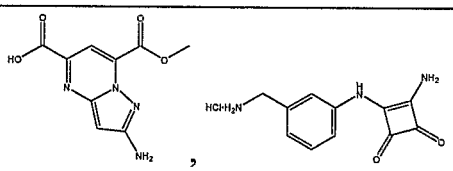
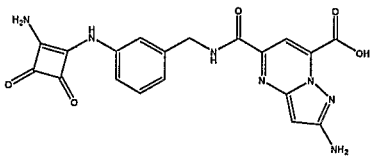
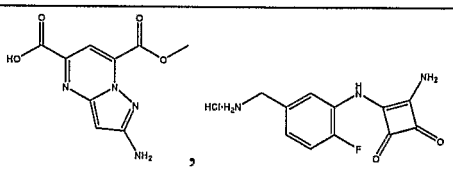
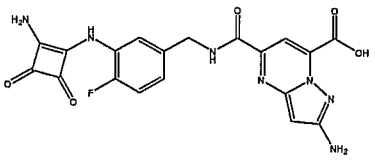
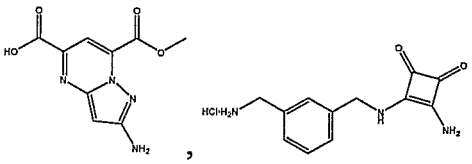
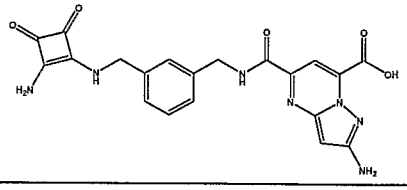
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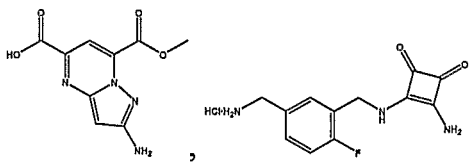
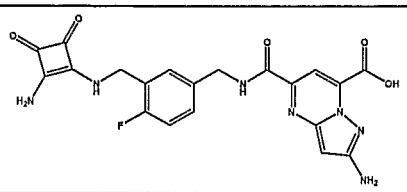
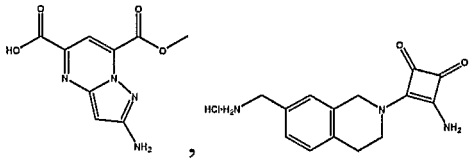
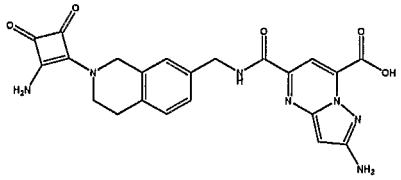
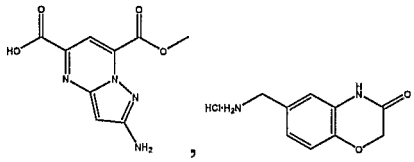
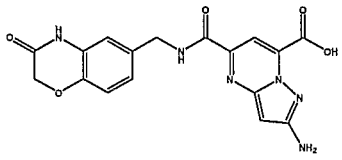
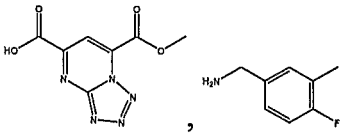
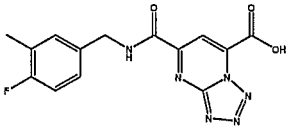
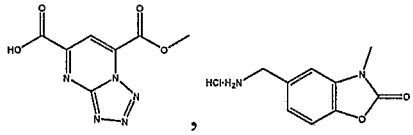
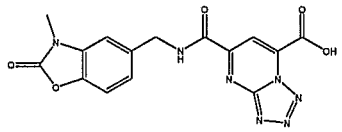
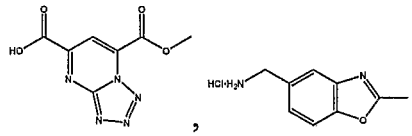
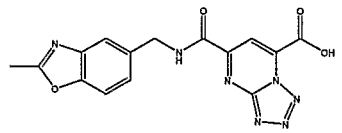
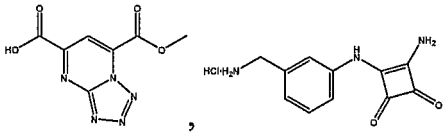
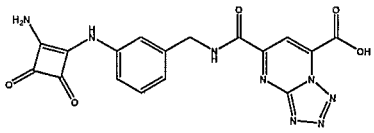
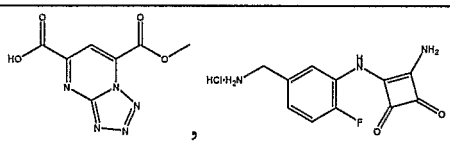
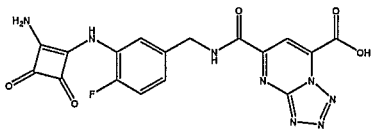
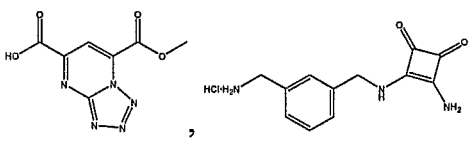
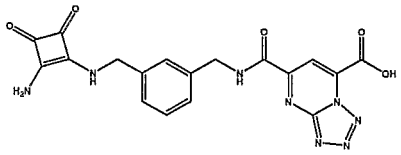
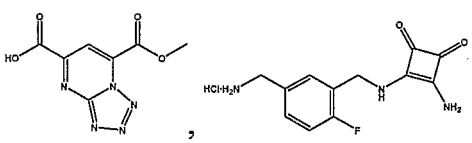
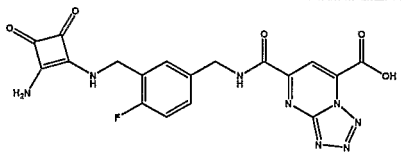
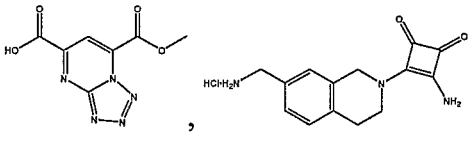
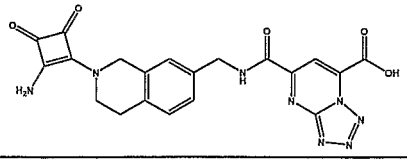
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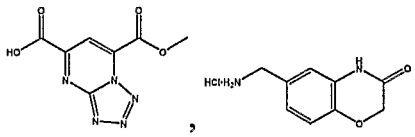
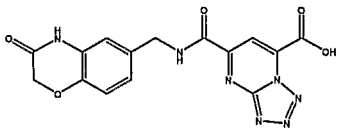
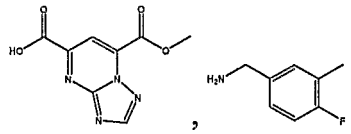
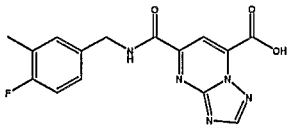
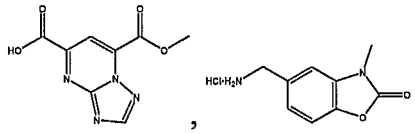
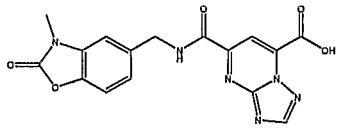
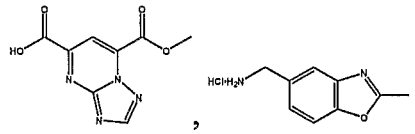
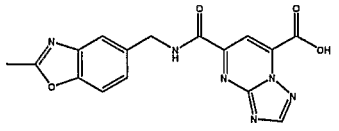
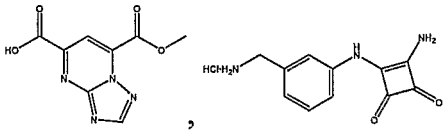
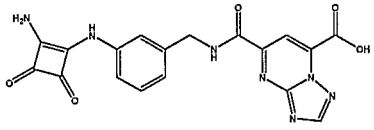
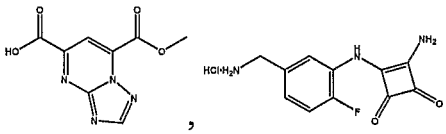
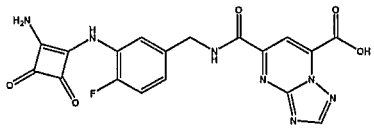
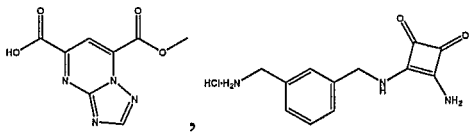
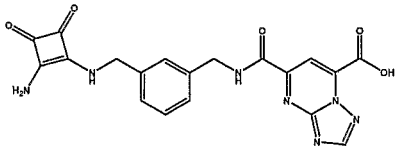
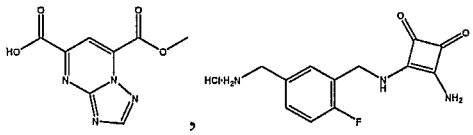
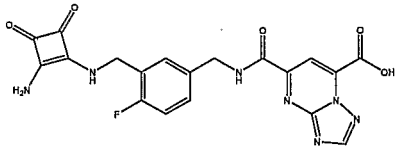
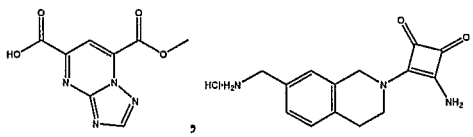
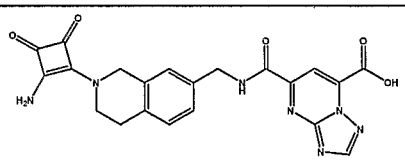
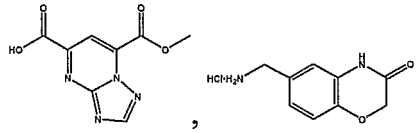
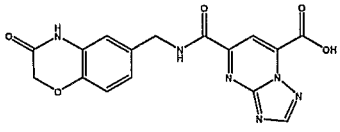
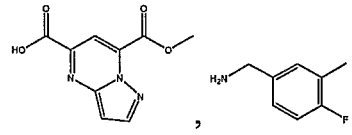
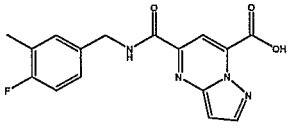
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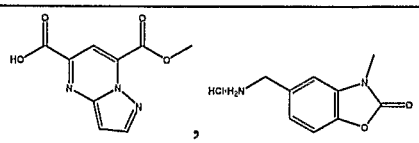
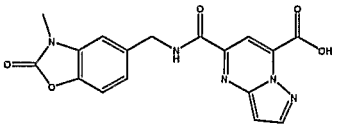
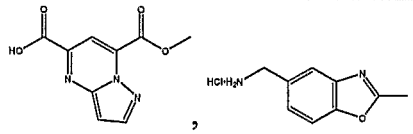
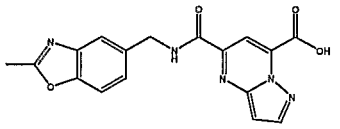
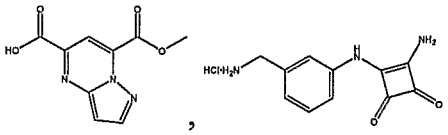
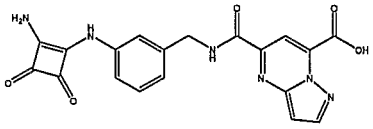
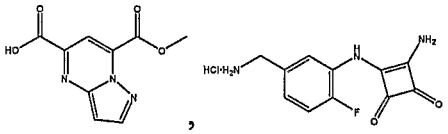
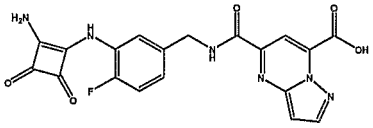
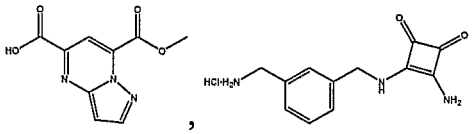
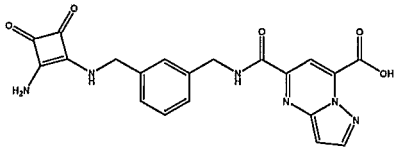
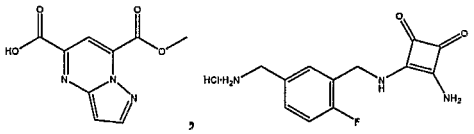
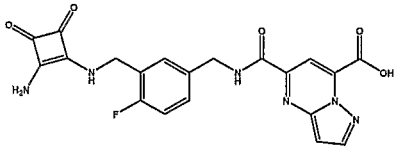
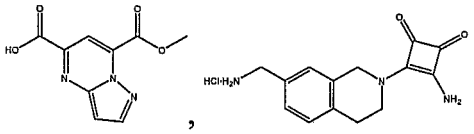
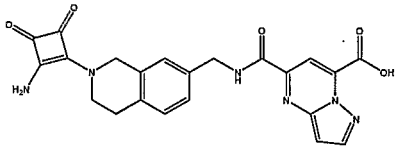
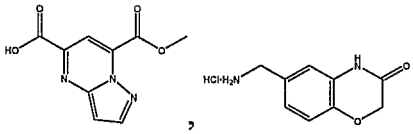
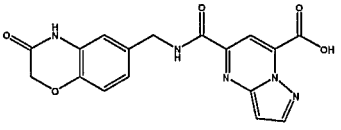
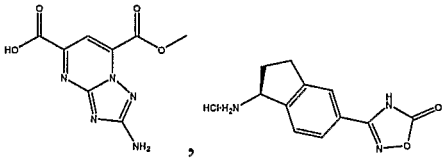
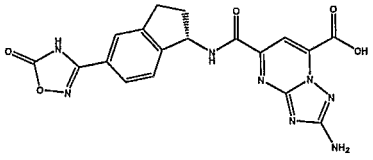
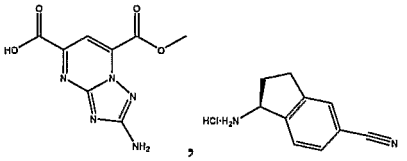
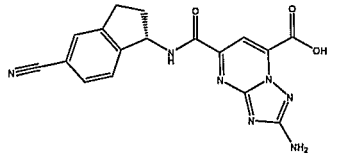
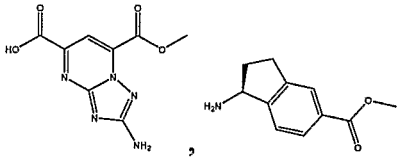
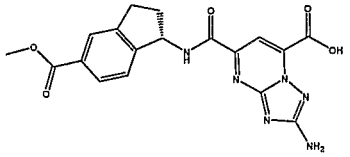
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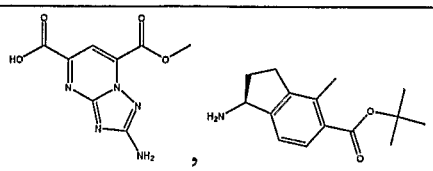
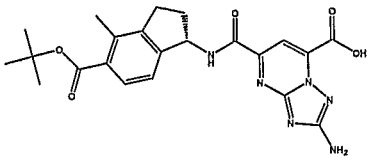
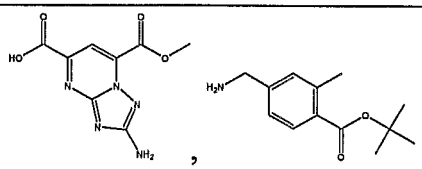
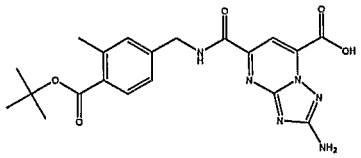
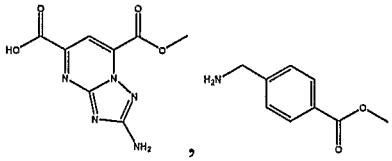
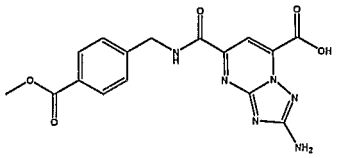
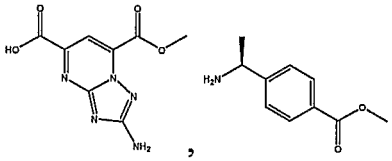
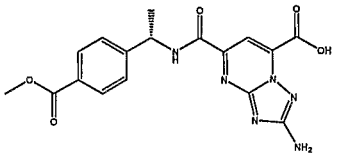
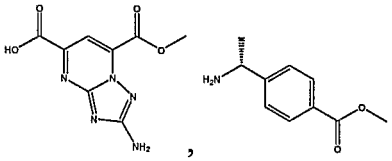
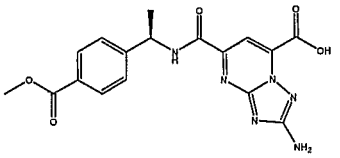
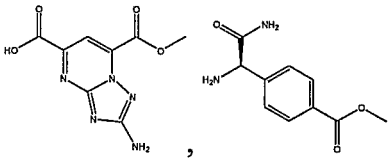
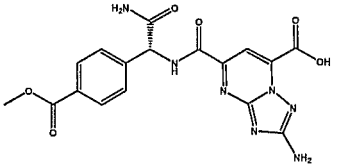
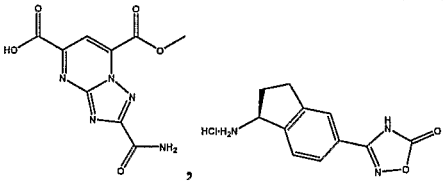
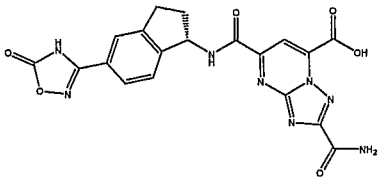
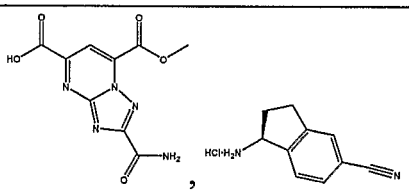
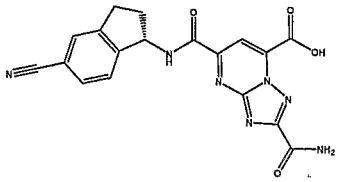
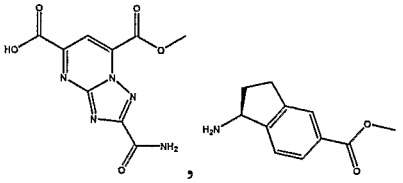
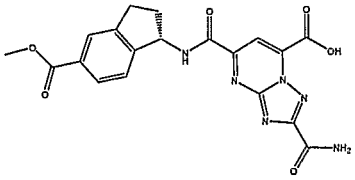
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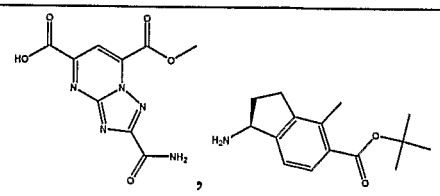
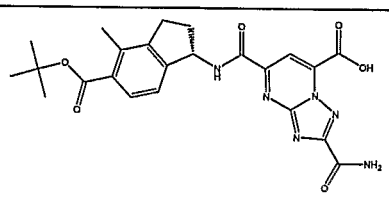
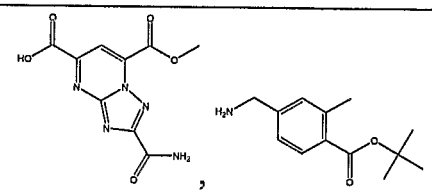
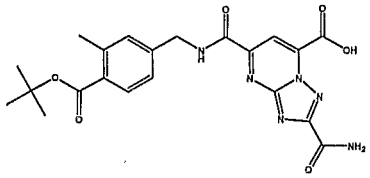
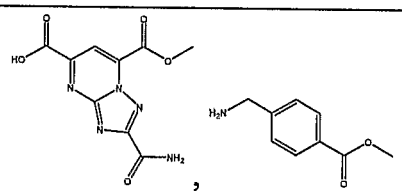
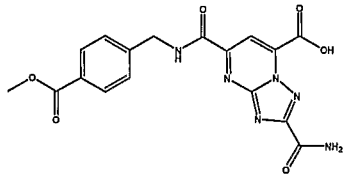
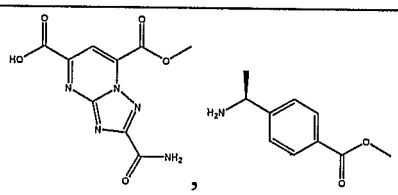
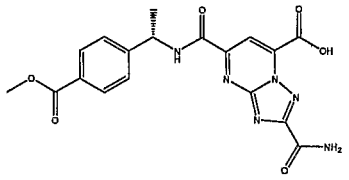
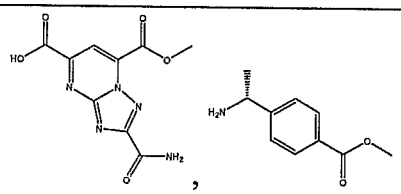
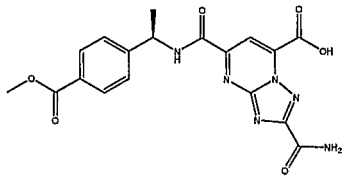
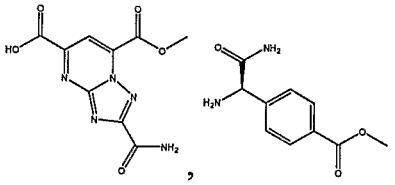
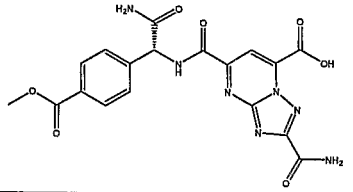
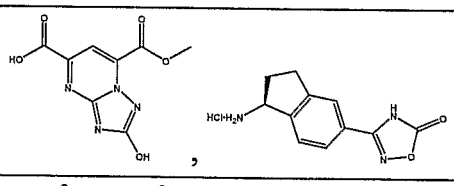
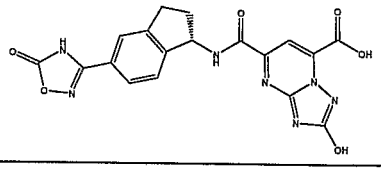
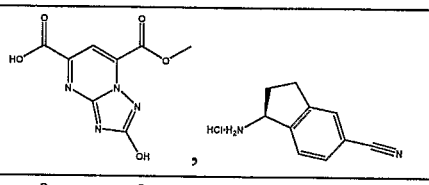
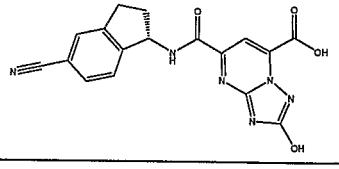
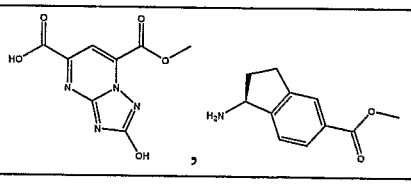
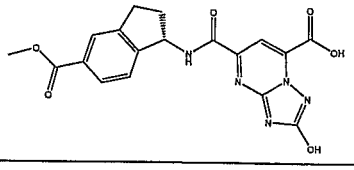
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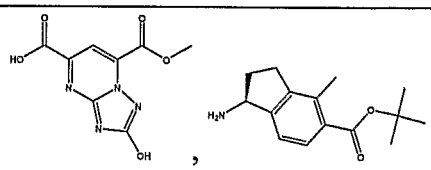
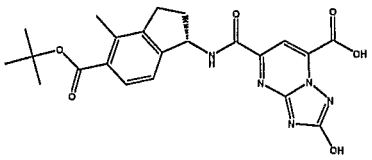
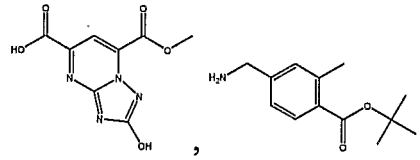
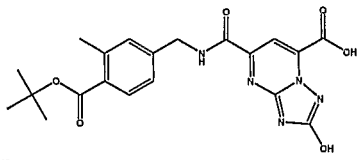
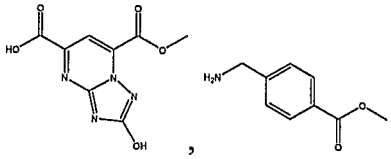
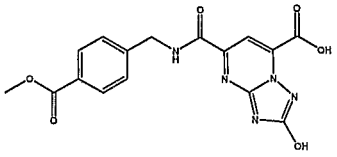
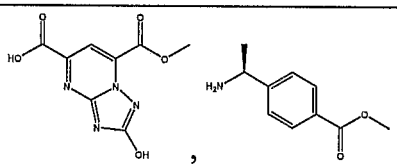
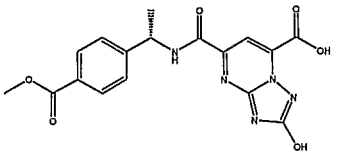
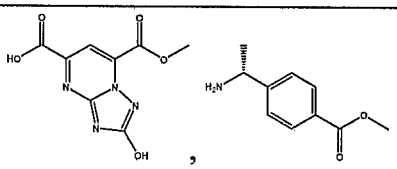
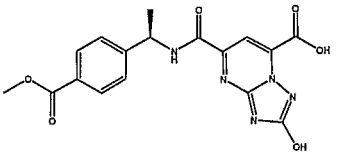
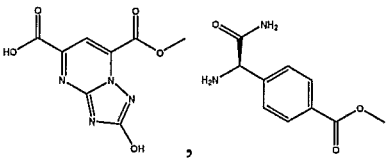
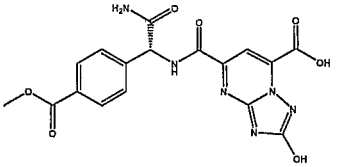
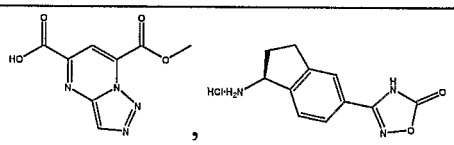
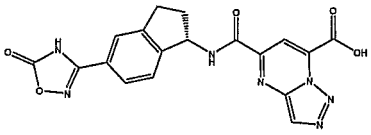
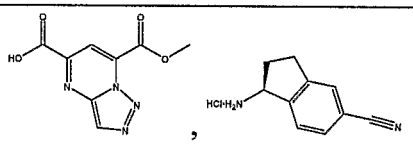
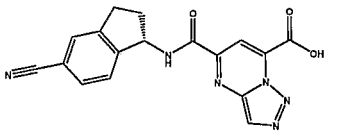
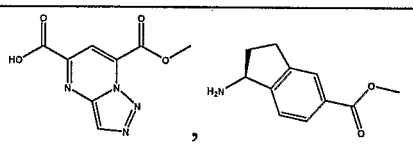
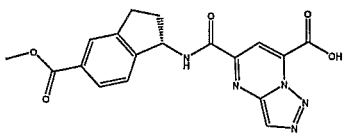
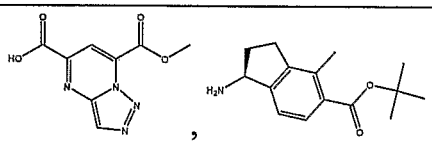
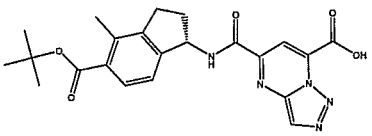
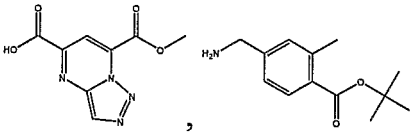
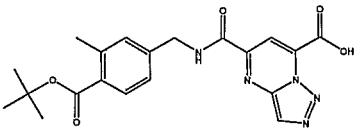
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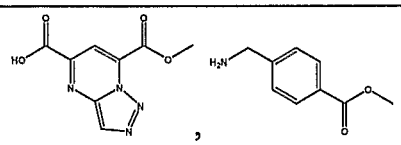
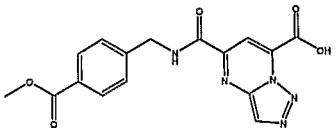
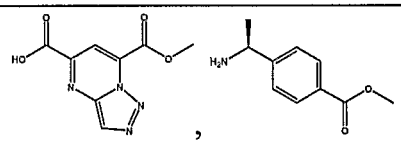
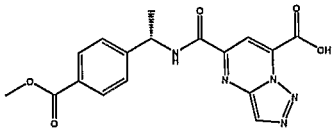
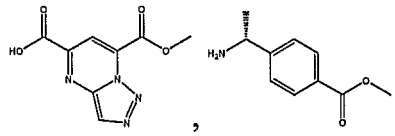
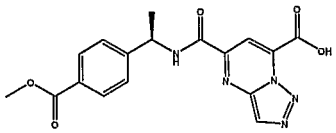
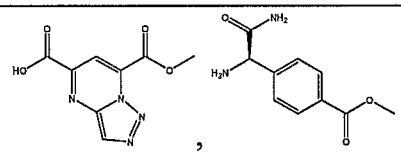
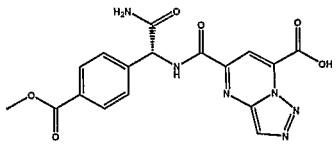
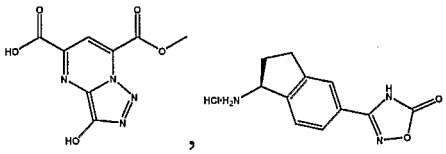
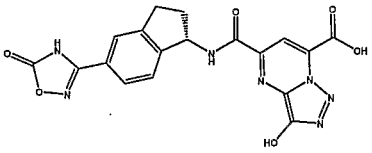
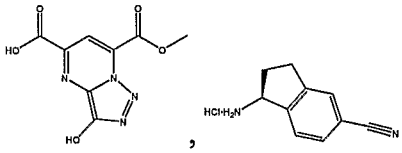
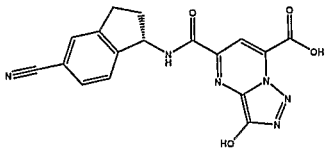
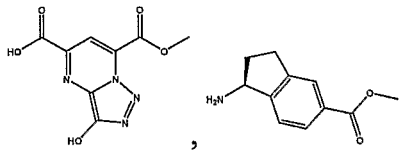
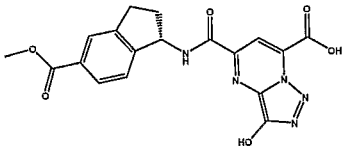
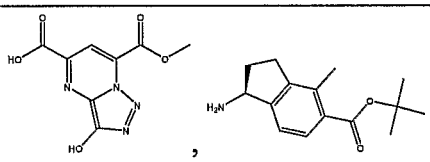
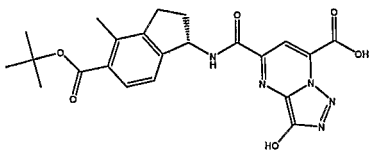
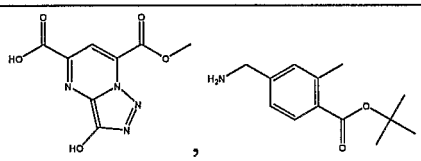
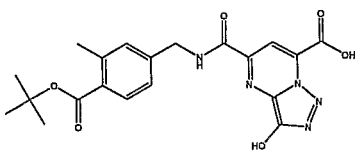
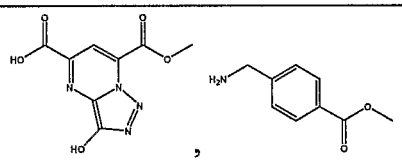
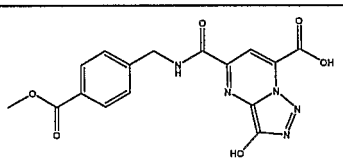
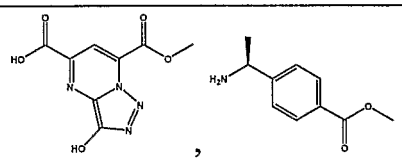
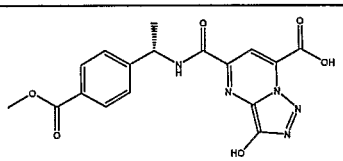
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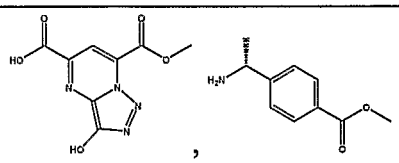
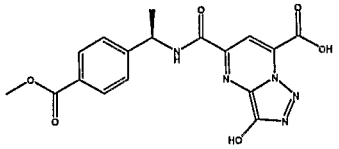
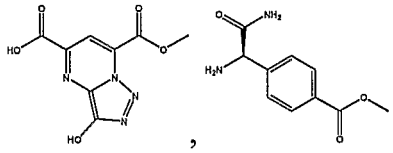
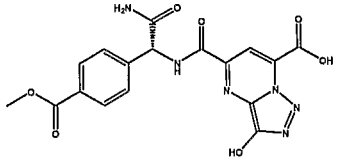
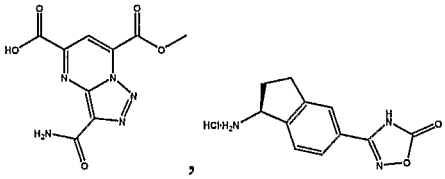
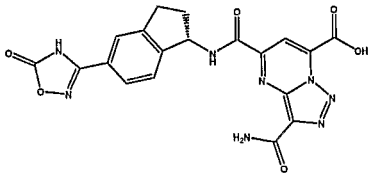
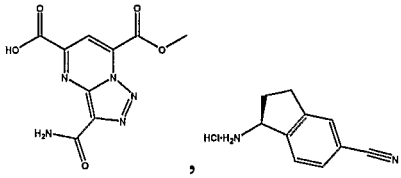
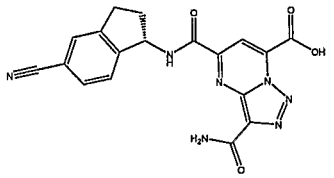
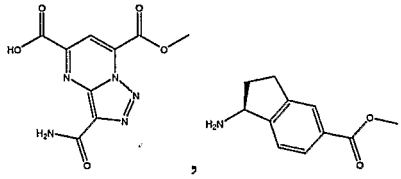
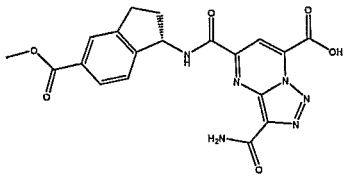
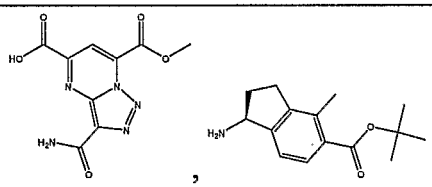
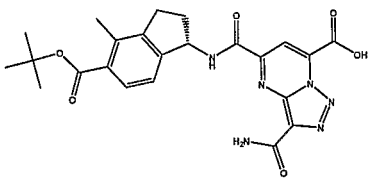
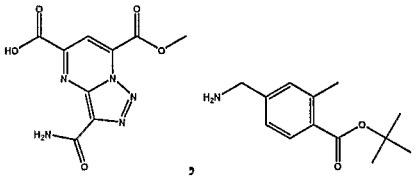
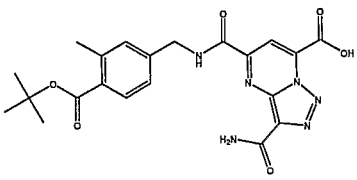
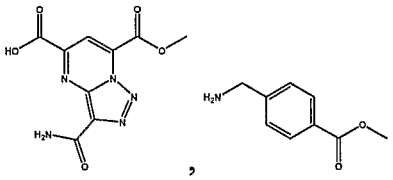
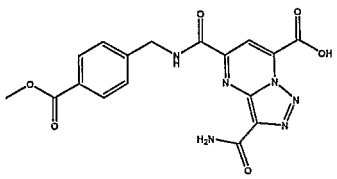
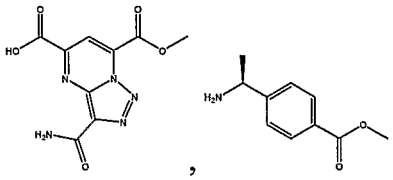
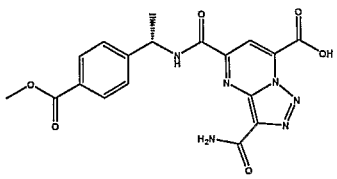
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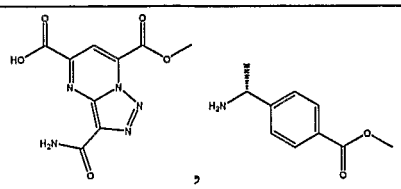
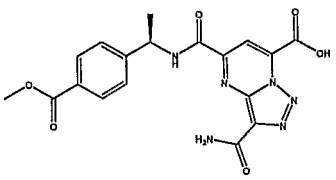
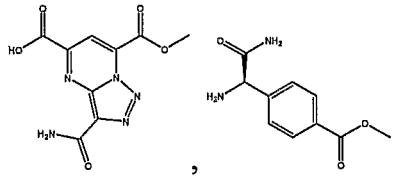
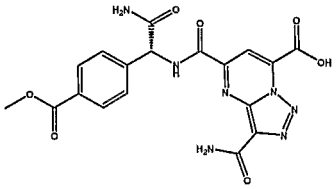
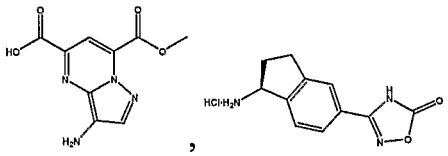
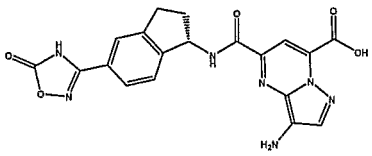
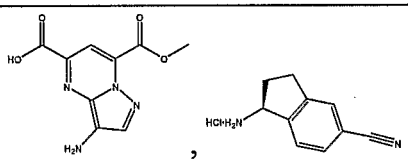
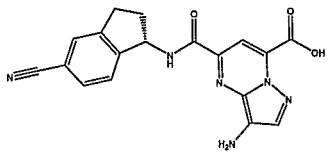
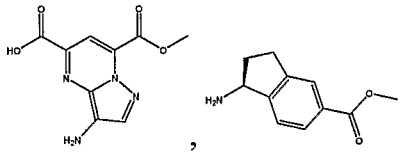
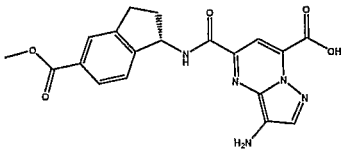
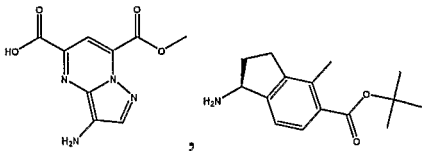
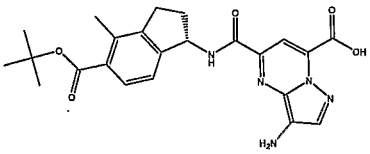
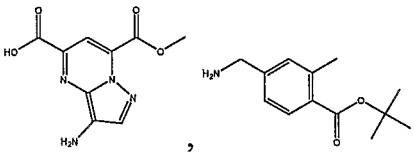
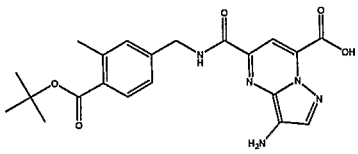
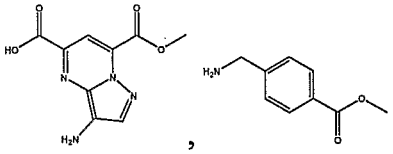
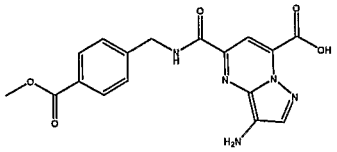
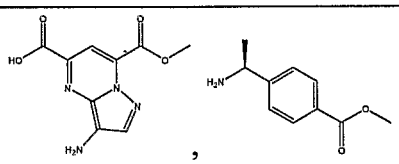
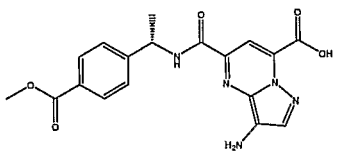
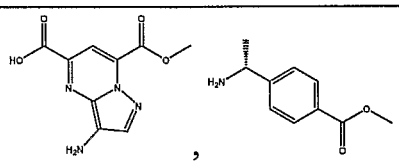
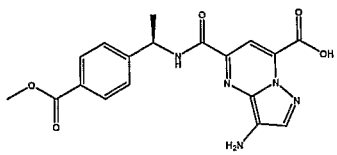
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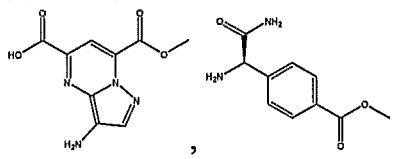
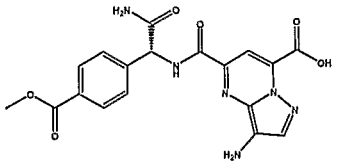
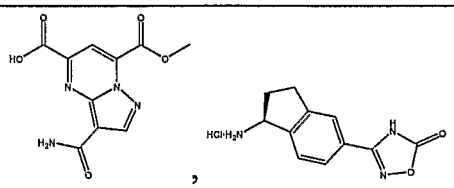
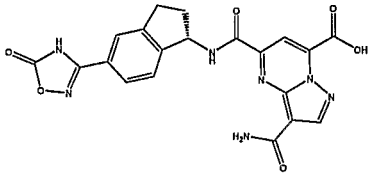
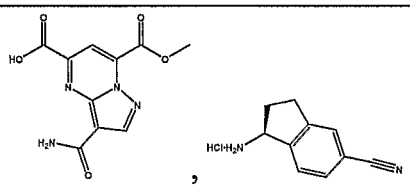
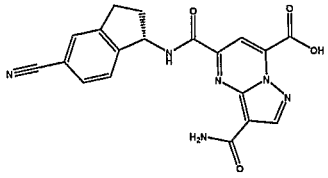
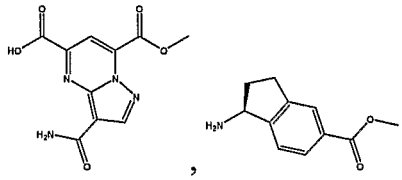
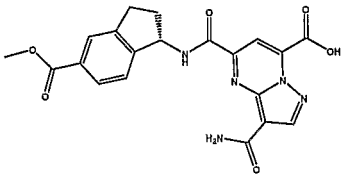
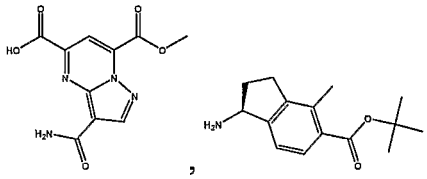
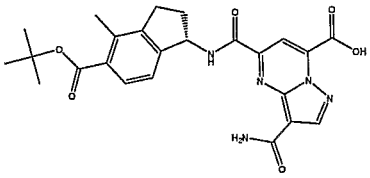
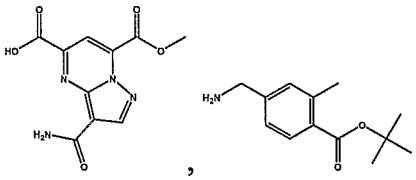
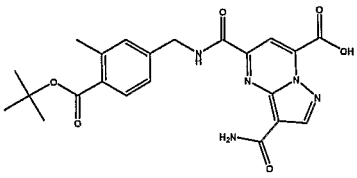
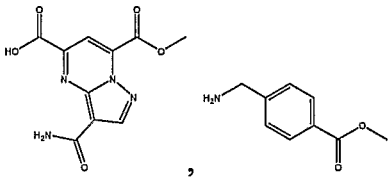
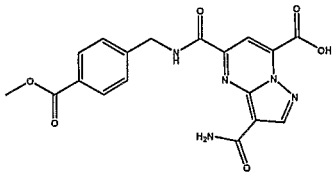
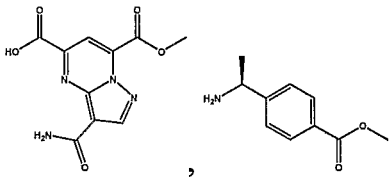
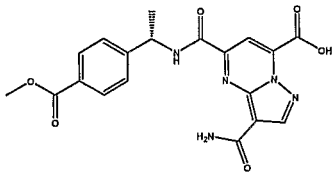
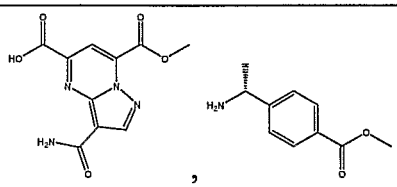
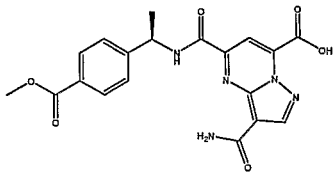
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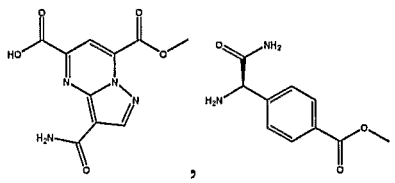
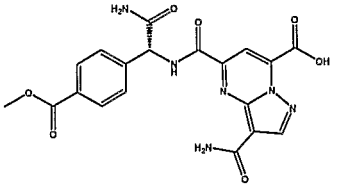
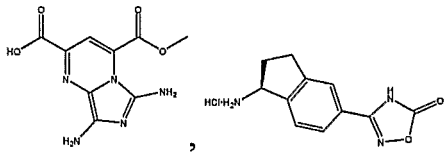
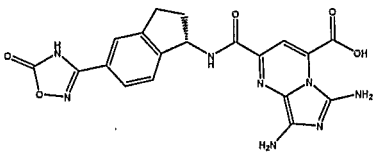
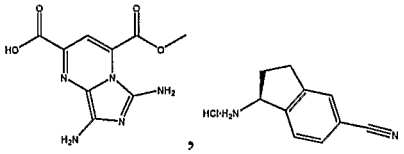
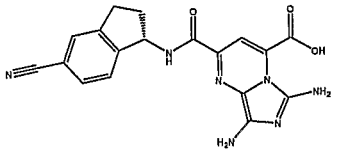
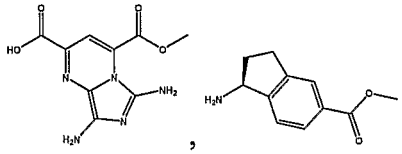
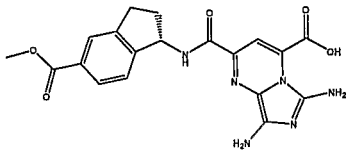
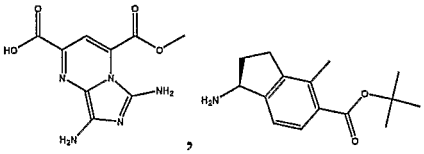
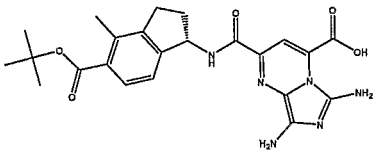
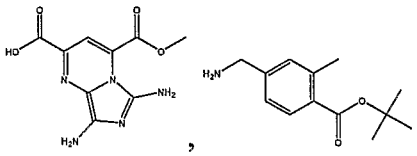
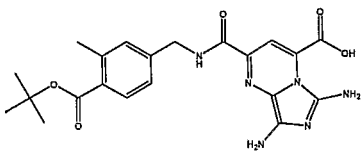
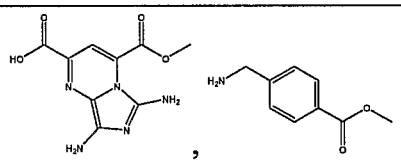
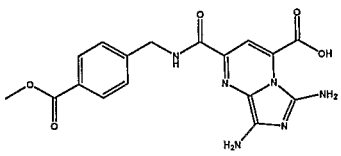
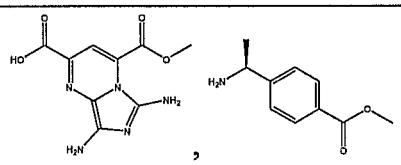
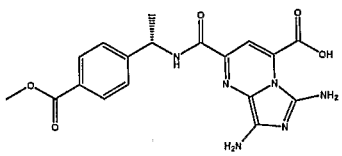
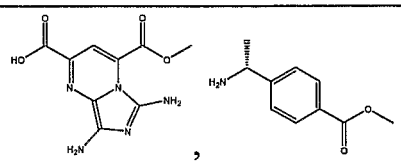
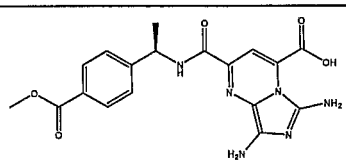
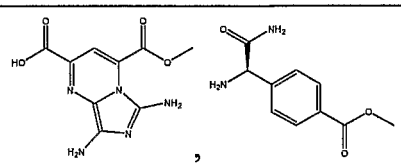
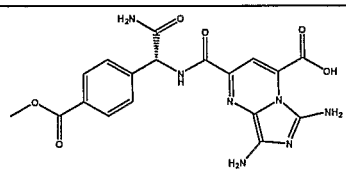
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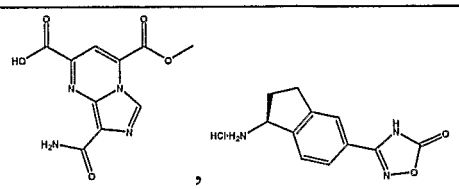
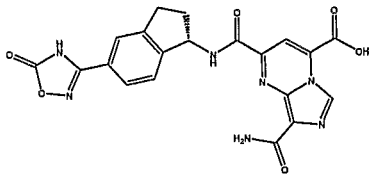
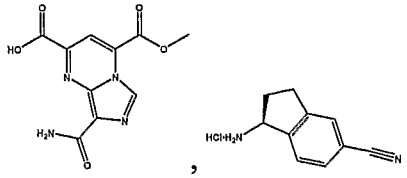
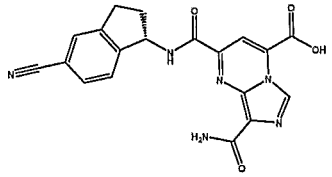
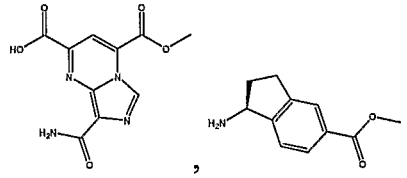
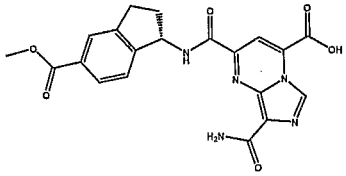
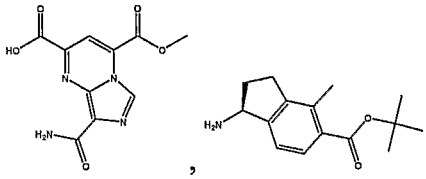
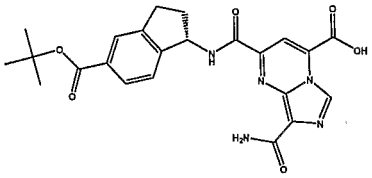
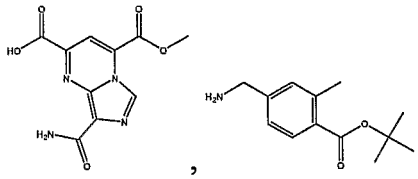
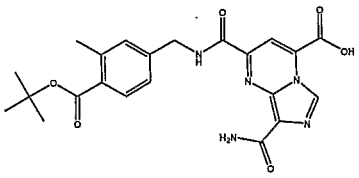
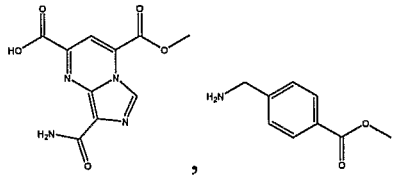
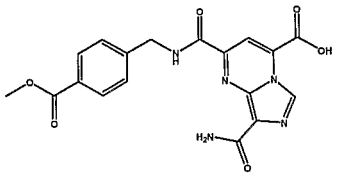
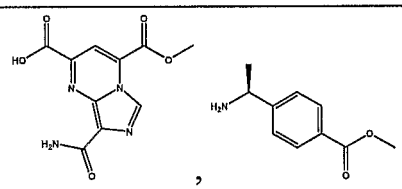
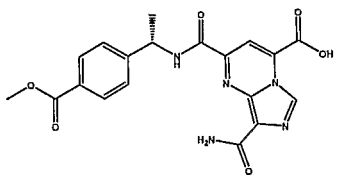
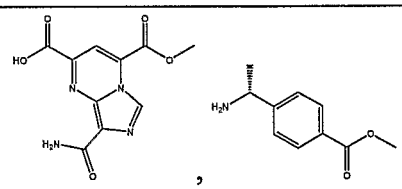
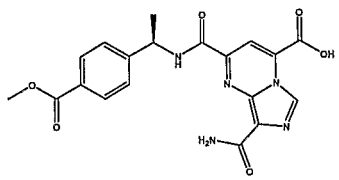
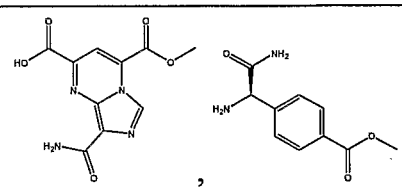
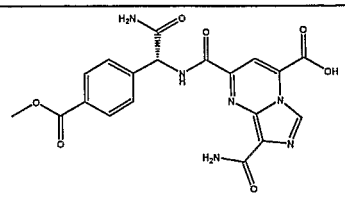
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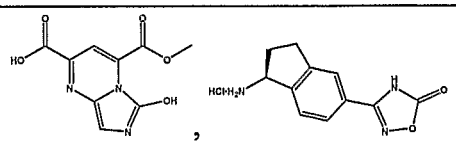
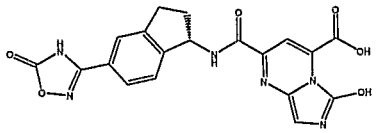
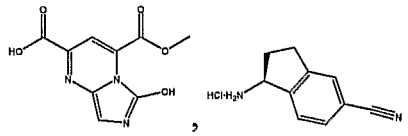
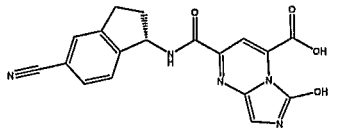
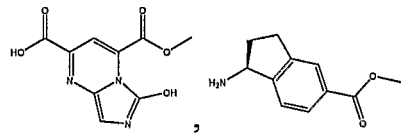
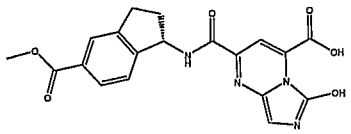
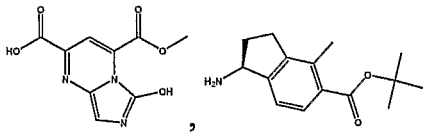
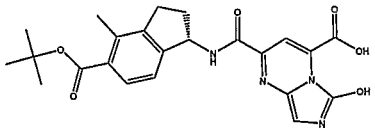
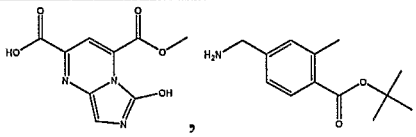
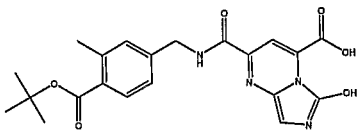
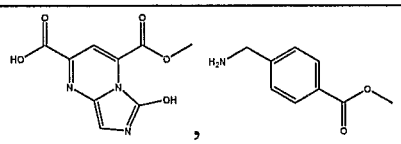
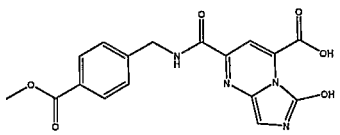
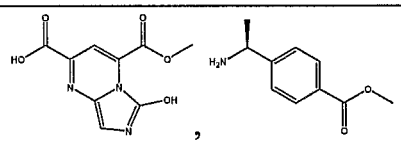
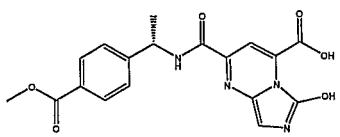
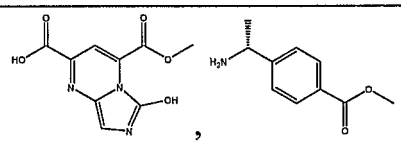
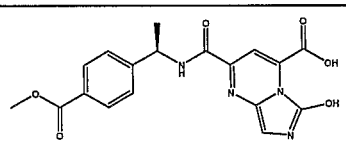
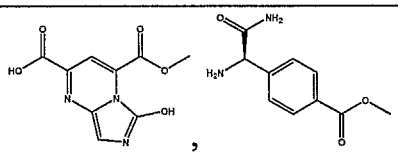
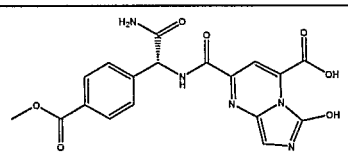
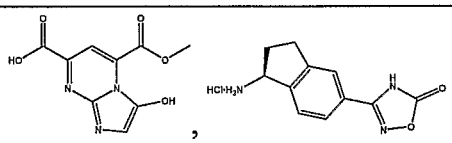
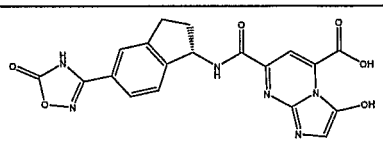
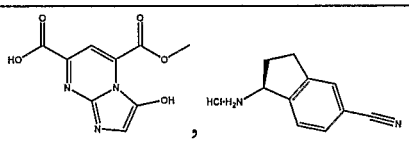
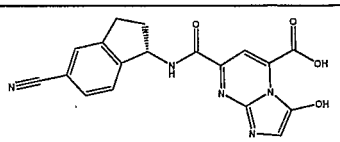
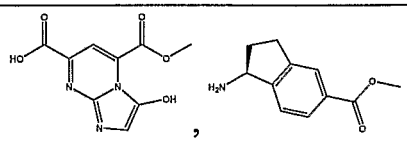
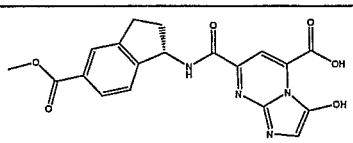
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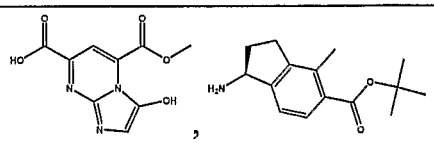
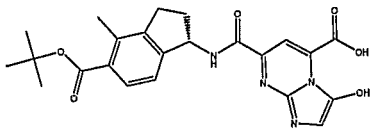
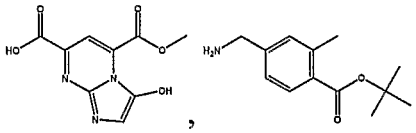
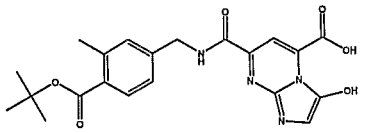
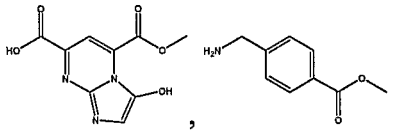
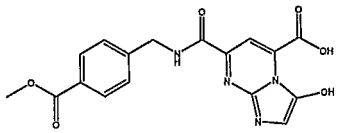
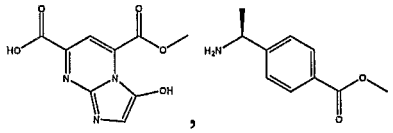
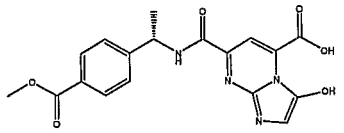
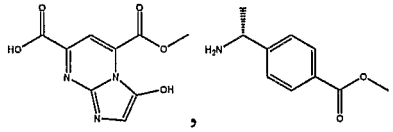
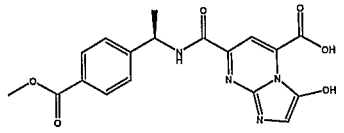
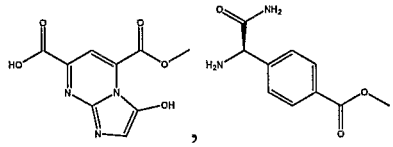
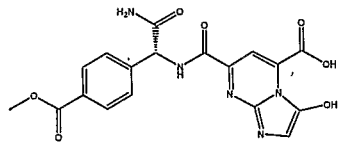
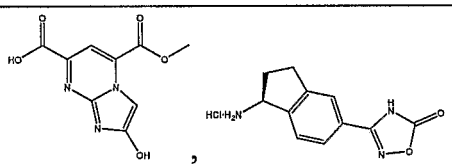
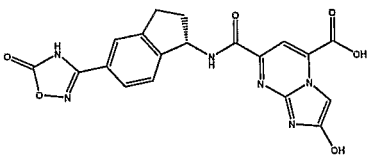
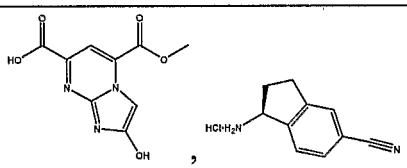
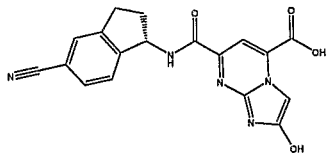
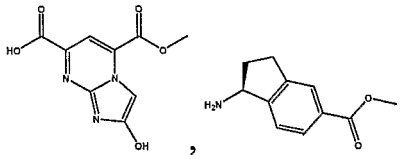
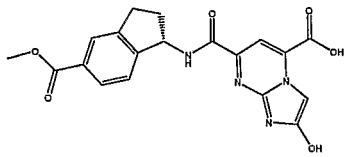
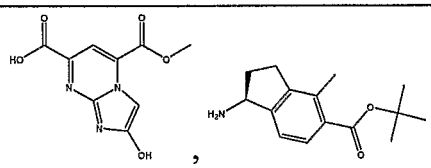
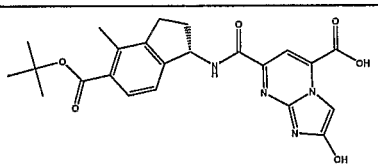
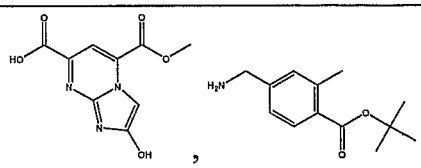
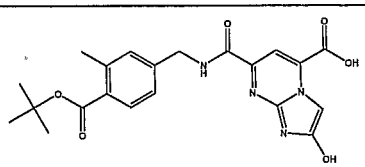
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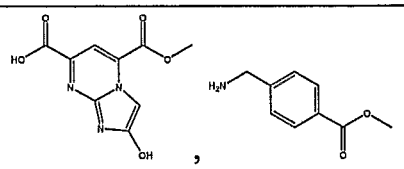
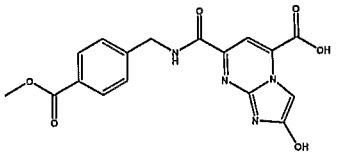
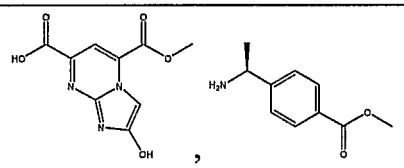
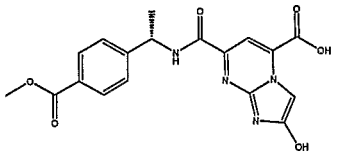
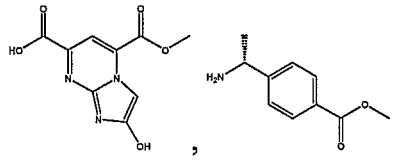
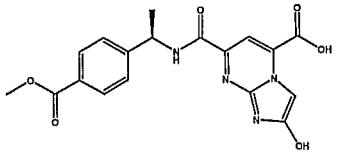
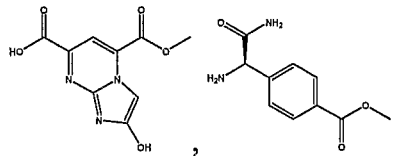
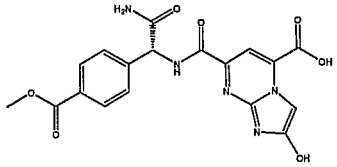
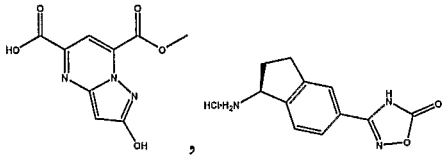
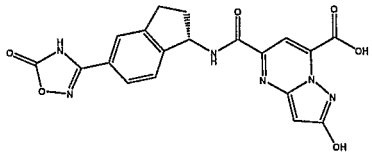
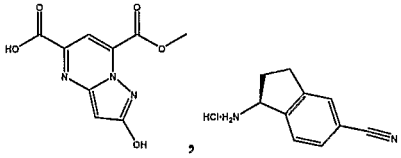
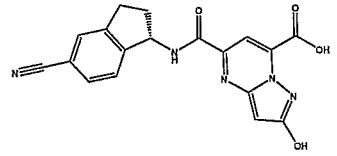
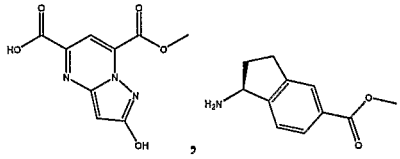
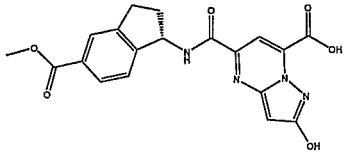
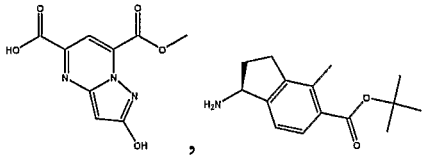
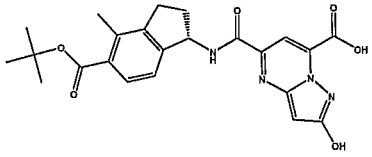
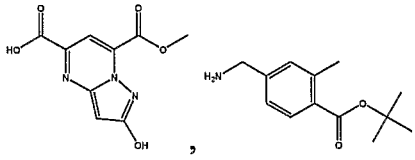
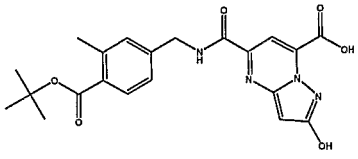
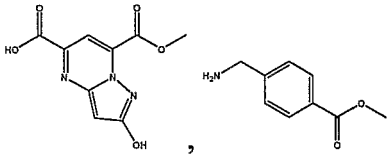
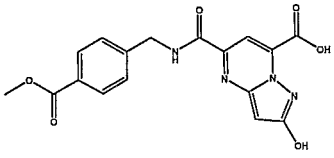
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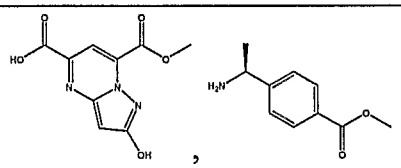
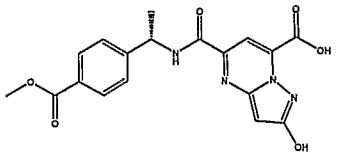
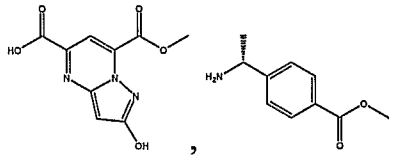
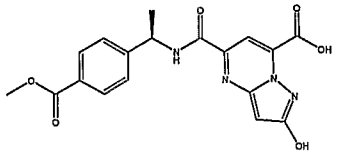
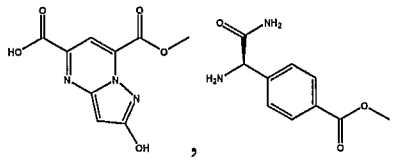
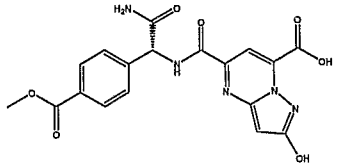
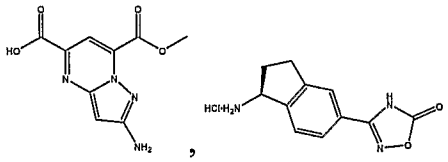
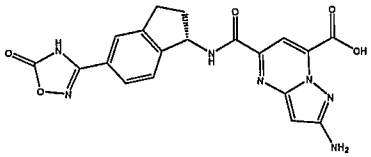
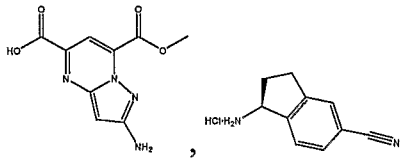
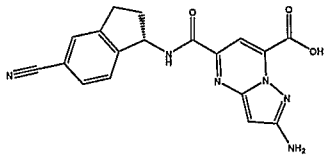
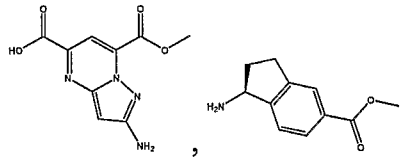
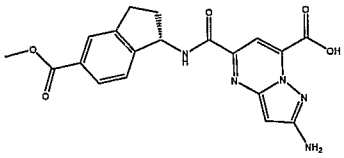
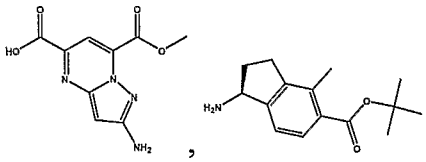
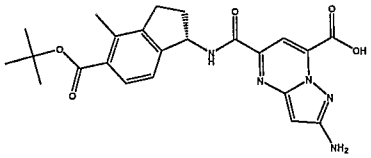
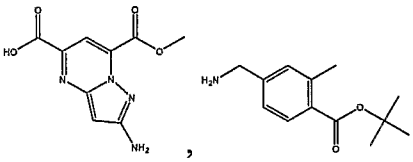
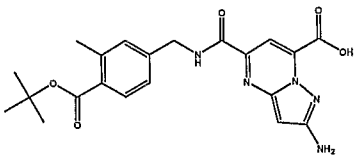
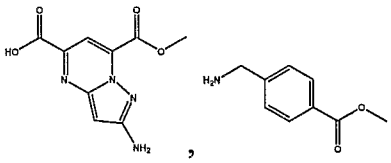
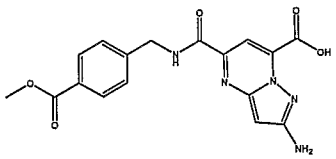
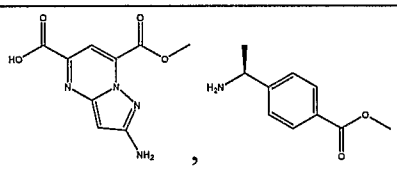
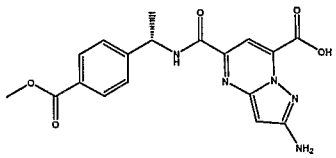
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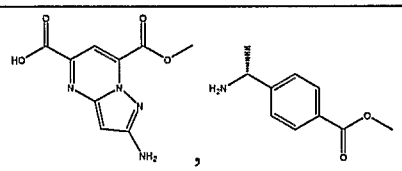
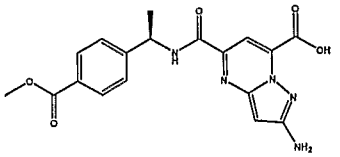
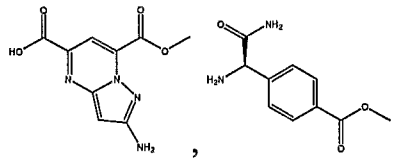
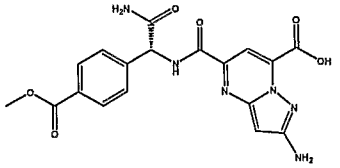
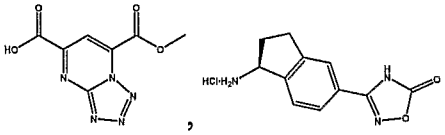
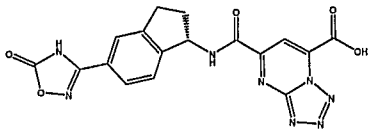
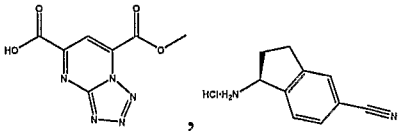
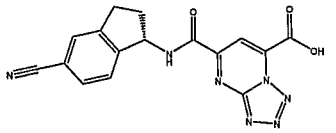
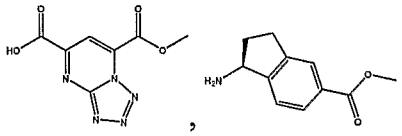
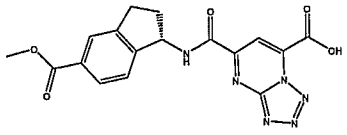
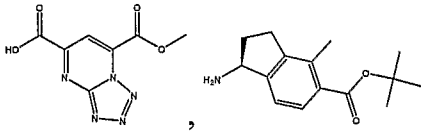
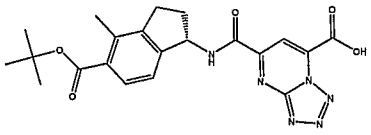
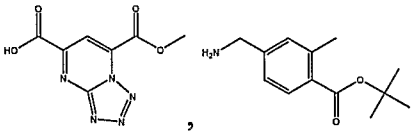
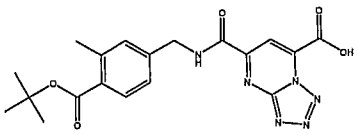
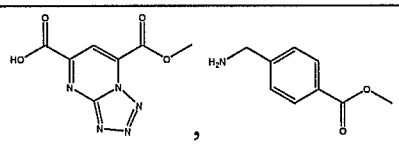
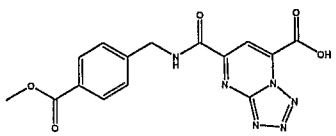
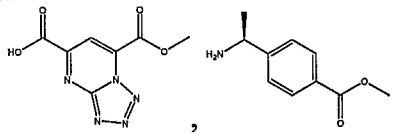
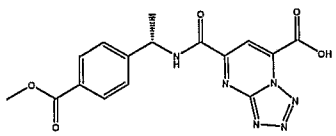
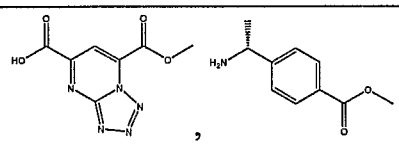
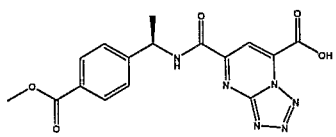
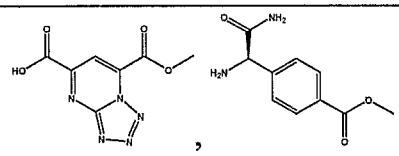
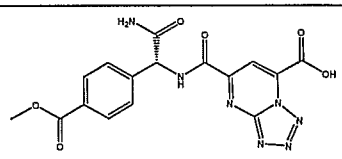
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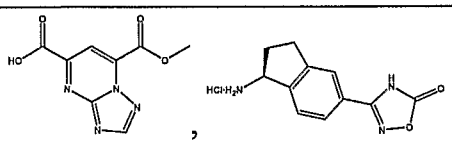
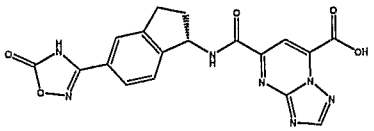
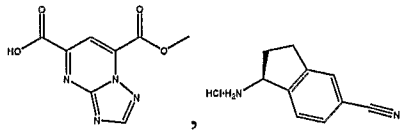
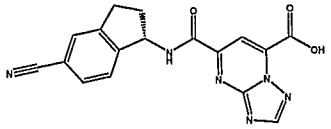
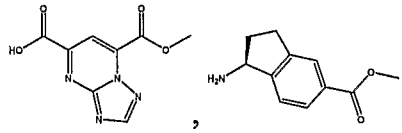
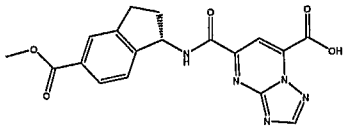
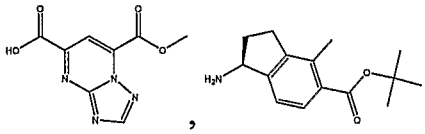
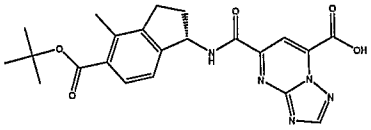
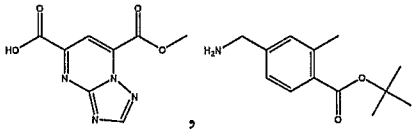
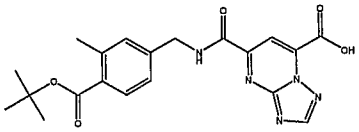
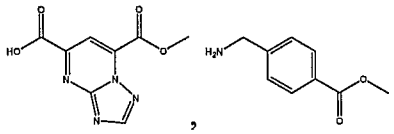
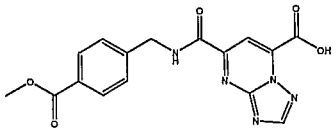
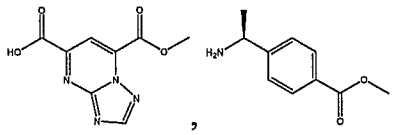
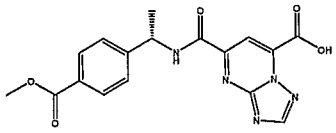
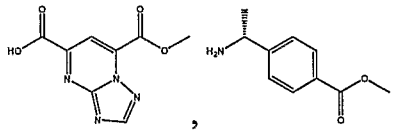
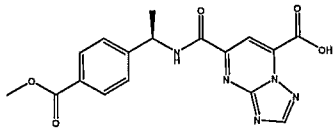
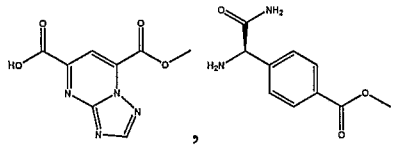
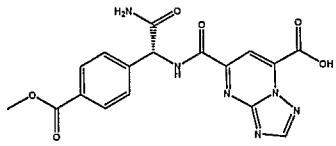
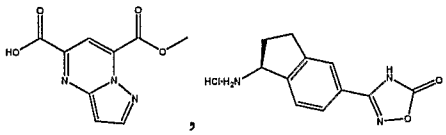
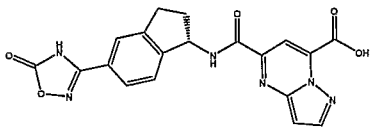
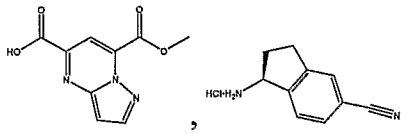
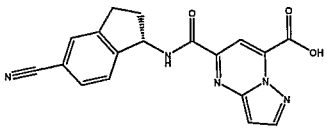
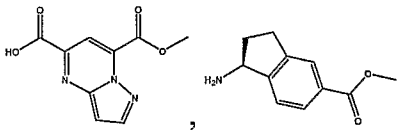
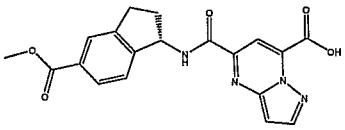
Prep. Ex. #	acid, amine	product
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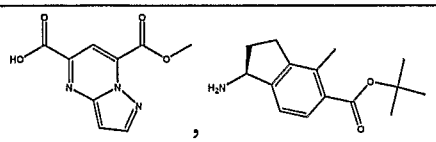
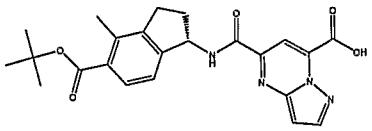
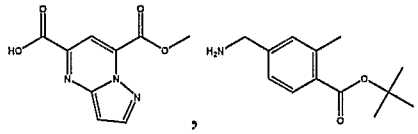
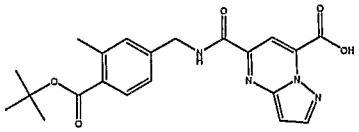
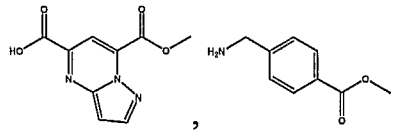
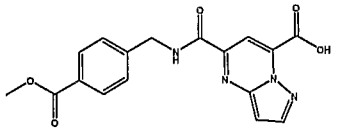
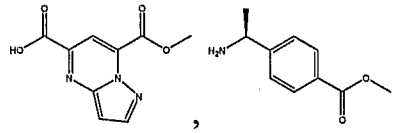
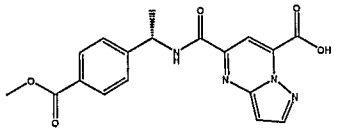
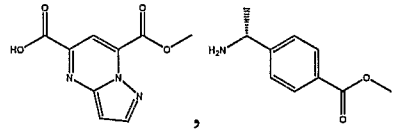
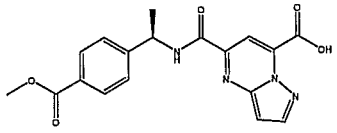
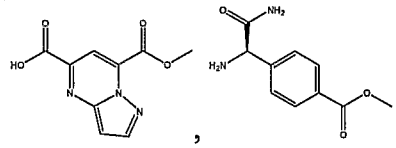
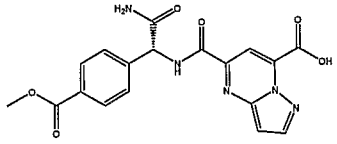
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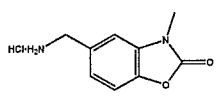
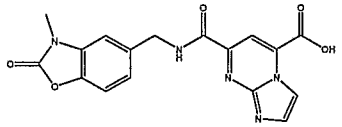
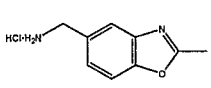
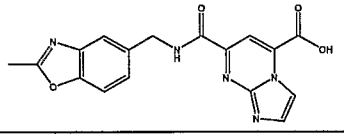
Prep. Ex. #	acid, amine	product
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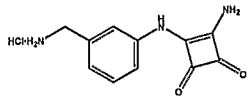
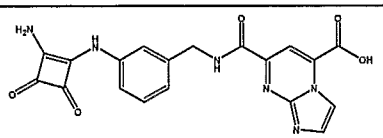
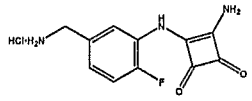
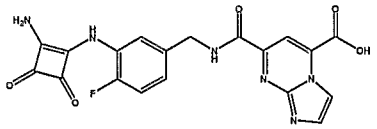
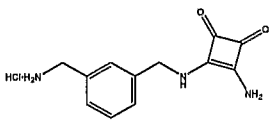
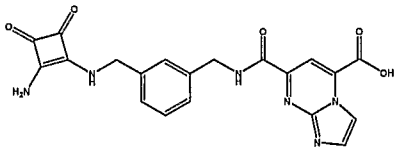
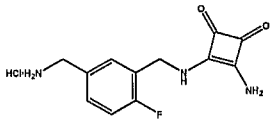
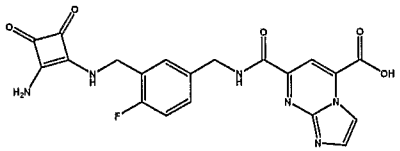
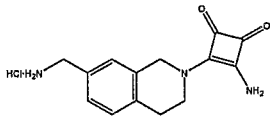
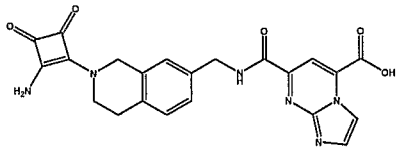
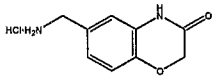
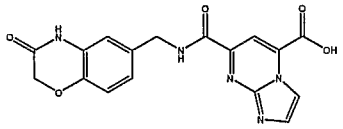
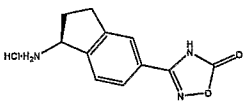
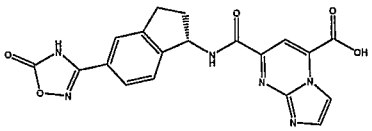
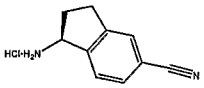
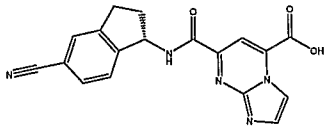
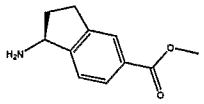
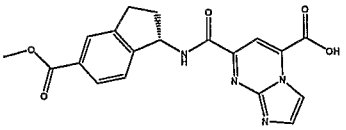
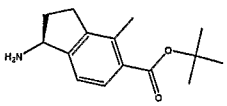
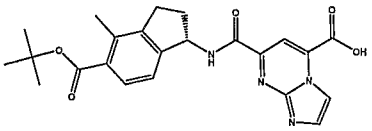
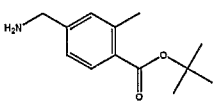
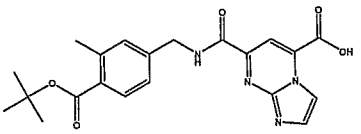
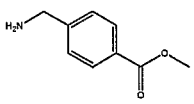
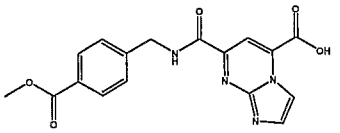
Prep. Ex. #	acid, amine	product
747		
748		
749		
750		
751		
752		

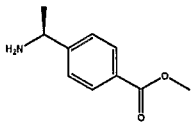
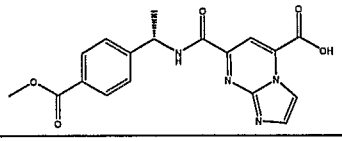
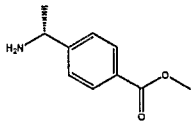
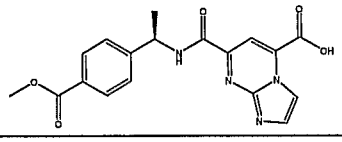
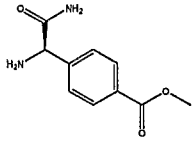
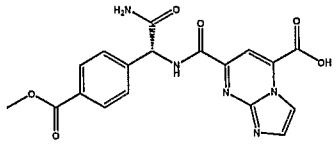
Preparative Example 753-769

[0520] If one were to follow a similar procedure as described in Preparative Example 322, Step B and Step C, except using the amines indicated in Table I-25 below in Step B, and if one were to treat the obtained esters similarly as described in the Preparative Examples 331, 332 or 333, the following compounds would be obtained.

Table I-25

Prep. Ex. #	amine	product
753		
754		

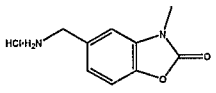
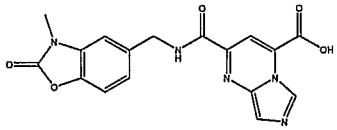
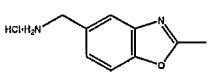
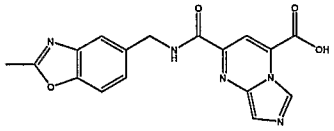
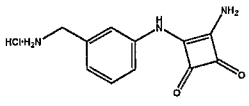
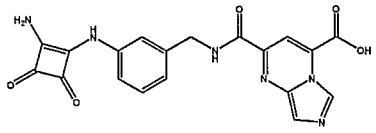
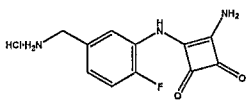
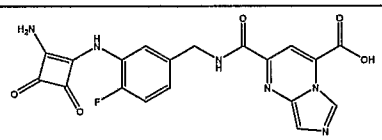
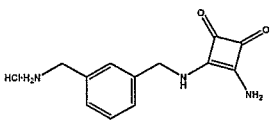
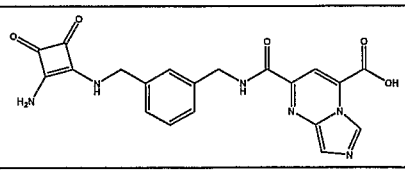
Prep. Ex. #	amine	product
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756		
757		
758		
759		
760		
761		
762		
763		
764		
765		
766		

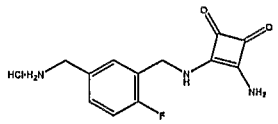
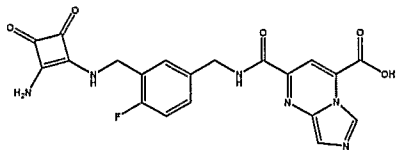
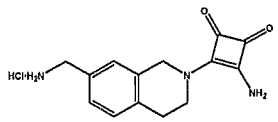
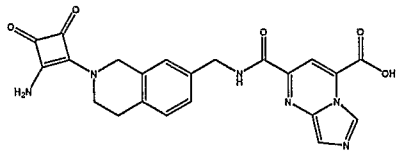
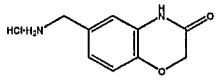
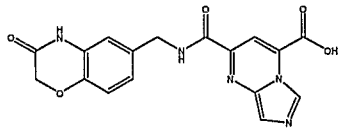
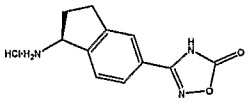
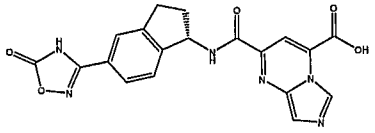
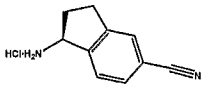
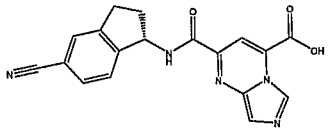
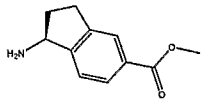
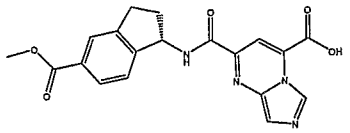
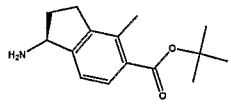
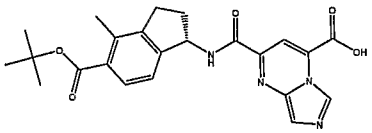
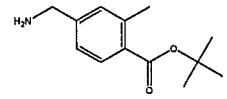
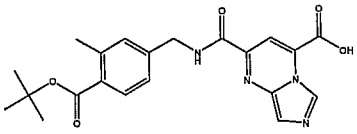
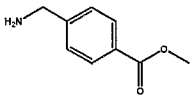
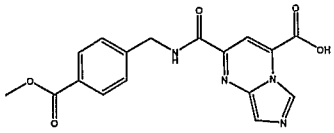
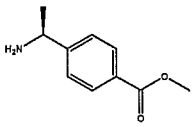
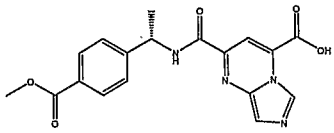
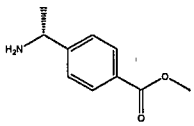
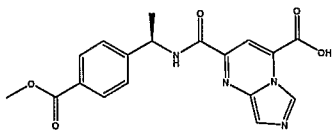
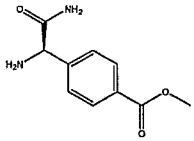
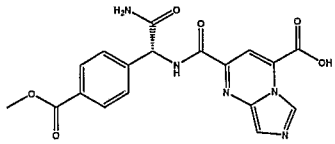
Prep. Ex. #	amine	product
767		
768		
769		

Preparative Example 770-786

[0521] If one were to follow a similar procedure as described in Preparative Example 323, Step B, except using the amines indicated in Table I-26 below, and if one were to treat the obtained esters similarly as described in the Preparative Examples 331, 332 or 333, the following compounds would be obtained.

Table I-26

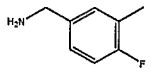
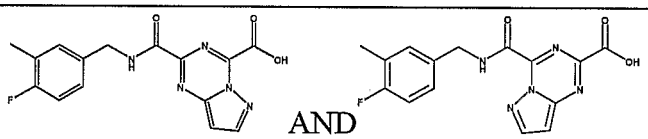
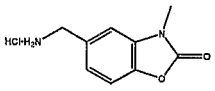
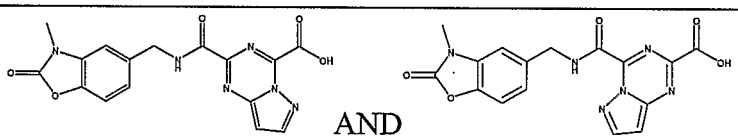
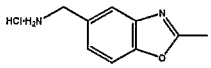
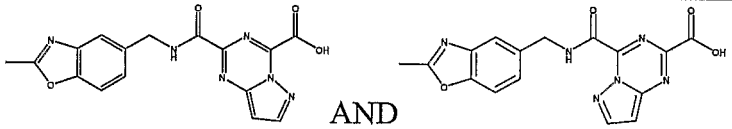
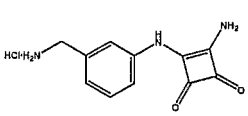
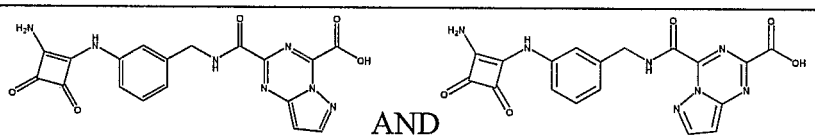
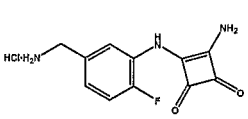
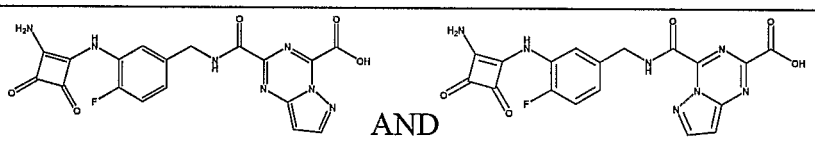
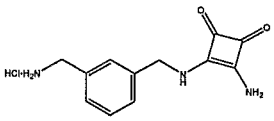
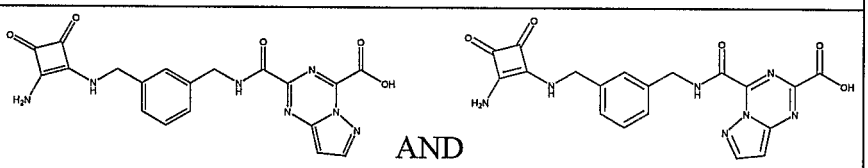
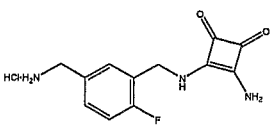
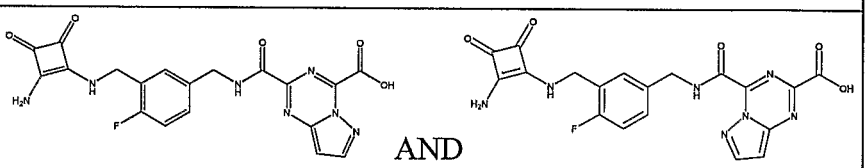
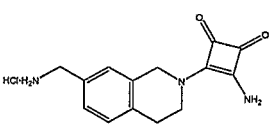
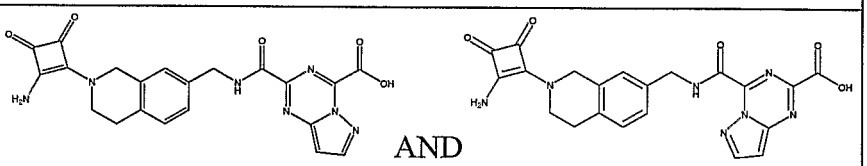
Prep. Ex. #	amine	product
770		
771		
772		
773		
774		

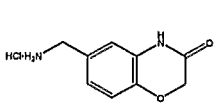
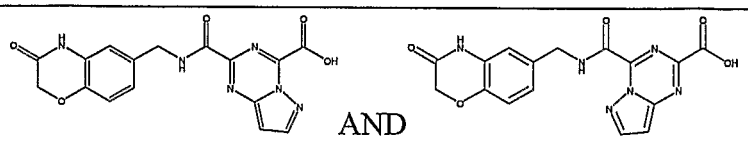
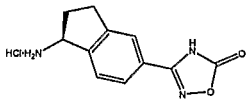
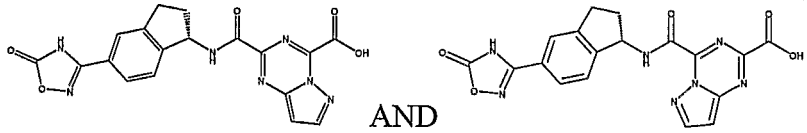
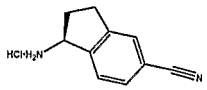
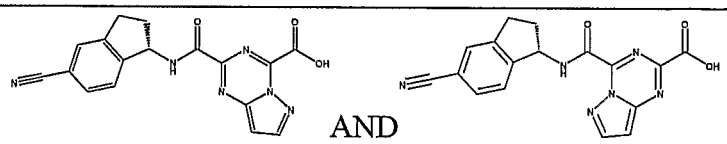
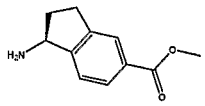
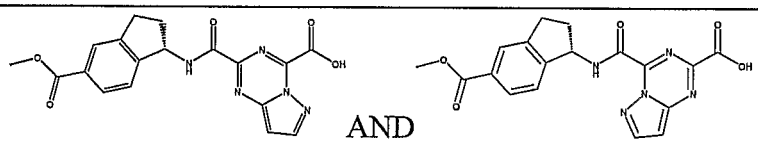
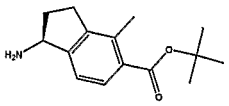
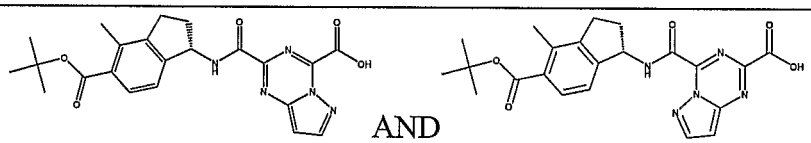
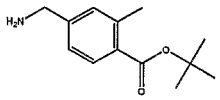
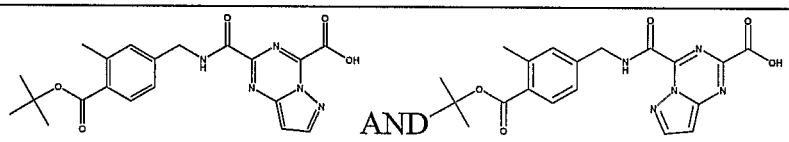
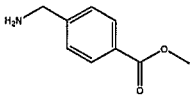
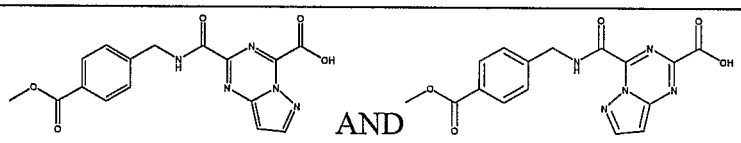
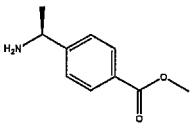
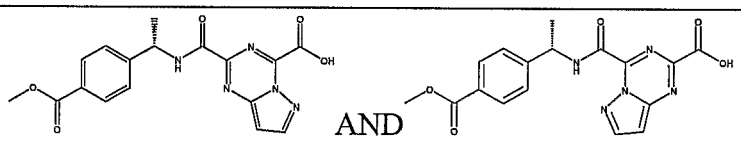
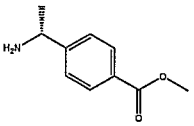
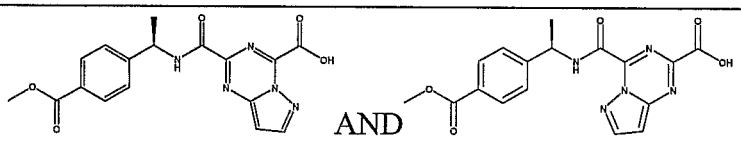
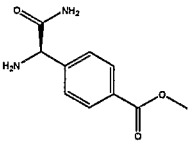
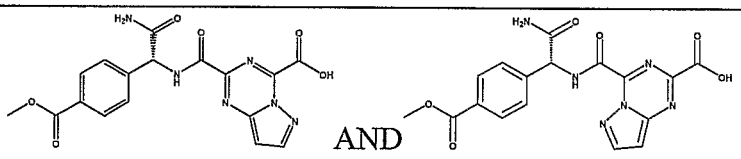
Prep. Ex. #	amine	product
775		
776		
777		
778		
779		
780		
781		
782		
783		
784		
785		
786		

Preparative Example 787-804

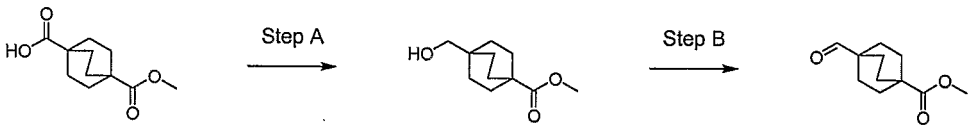
[0522] If one were to follow a similar procedure as described in Preparative Example 330, Step B, except using the amines indicated in Table I-27 below, and if one were to treat the obtained esters similarly as described in the Preparative Examples 331, 332 or 333, the following compounds would be obtained.

Table I-27

Prep. Ex. #	amine	products
787		 AND
788		 AND
789		 AND
790		 AND
791		 AND
792		 AND
793		 AND
794		 AND

Prep. Ex. #	amine	products
795		
796		
797		
798		
799		
800		
801		
802		
803		
804		

Preparative Example 805



[0523] Step A

To a cooled (–40°C) solution of the title compound from the Preparative Example 39, Step C (1.0 g) and NEt_3 (890 μL) in THF (50 mL) was slowly added ethyl chloroformate (490 μL). The mixture was stirred at –25°C for 1 h and then filtered. The precipitated salts were washed with THF (40 mL). The combined filtrates were cooled to 0°C and a solution of $NaBH_4$ (528 mg) in H_2O (9.4 mL) was added carefully. The mixture was stirred at 0°C for 45 min, the cooling bath was removed and stirring was continued at room temperature for 45 min. Then the mixture was diluted with saturated aqueous $NaHCO_3$ (40 mL) and saturated aqueous NaCl (40 mL). The organic phase was separated, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/acetone) to afford the title compound (910 mg, 97%). $[MH]^+ = 199$.

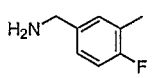
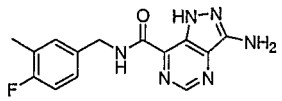
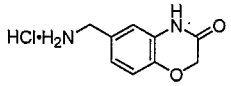
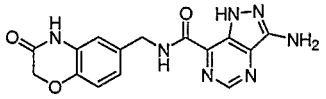
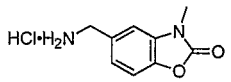
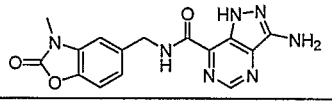
[0524] Step B

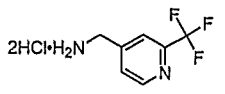
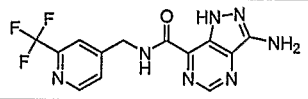
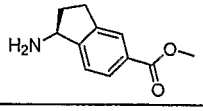
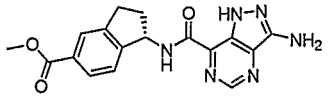
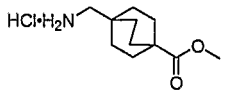
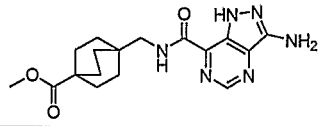
If one were to stir a mixture of the title compound from Step A above and IBX-polystyrene (1.75 equivalents) in CH_2Cl_2 at room temperature for 3 h, filter and concentrate the mixture, one would obtain the title compound.

Preparative Examples 806-811

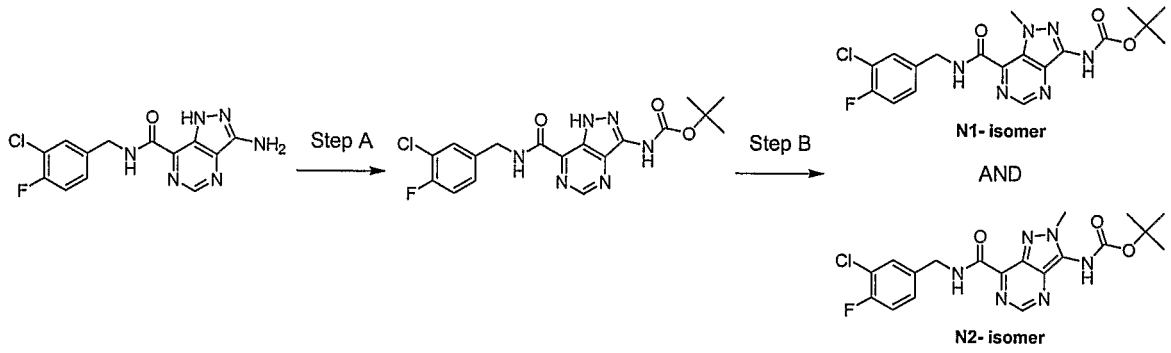
[0525] If one were to follow a similar procedure as described in the Preparative Example 377, except using the amines indicated in Table I-28 below, the following compounds would be obtained.

Table I-28

Prep. Ex. #	amine	product
806		
807		
808		

Prep. Ex. #	amine	product
809		
810		
811		

Preparative Examples 812



[0526] Step A

If one were to stir a mixture of the title compound from the Preparative Example 377, Step E, di-*tert*-butyl dicarbonate (1 equivalent) and NEt_3 in THF at room temperature overnight, concentrate the mixture and purify the residue by chromatography (silica), one would obtain the title compound.

[0527] Step B

If one were to stir a mixture of the title compound from Step A above, iodomethane and K_2CO_3 in DMF at room temperature overnight, concentrate the mixture and purify the residue by chromatography (silica), one would obtain the separated regioisomers of the title compound.

Preparative Examples 813



[0528] Step A

If one were to stir the N1-isomer of title compound from the Preparative Example 812, Step B in a 4M solution of HCl in 1,4-dioxane at room temperature overnight and concentrate the mixture, one would obtain the title compound.

Preparative Examples 814



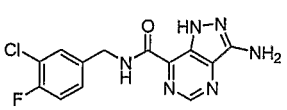
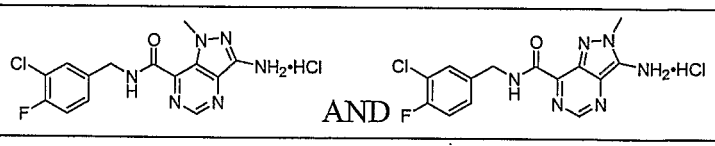
[0529] Step A

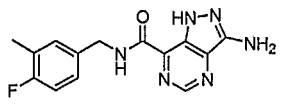
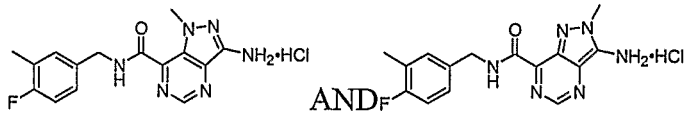
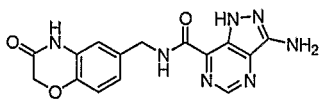
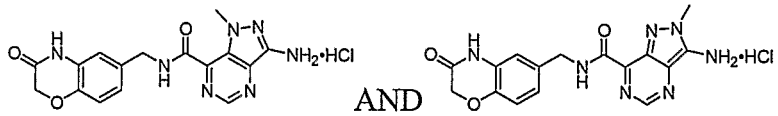
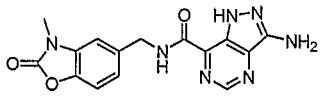
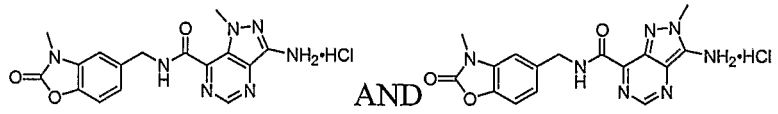
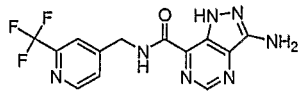
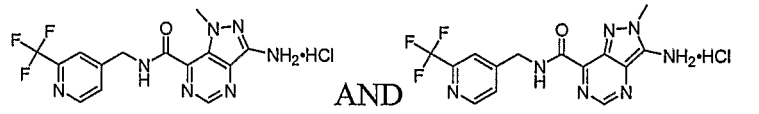
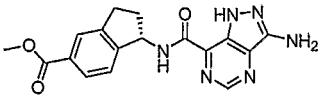
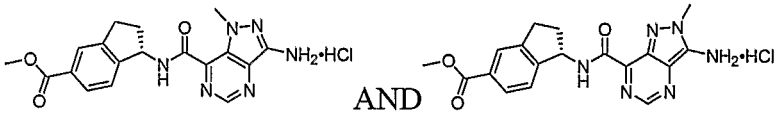
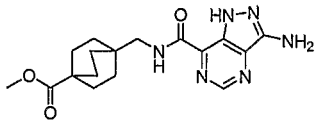
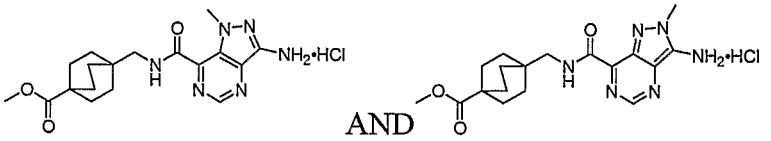
If one were to stir the N2-isomer of title compound from the Preparative Example 812, Step B in a 4M solution of HCl in 1,4-dioxane at room temperature overnight and concentrate the mixture, one would obtain the title compound.

Preparative Examples 815-821

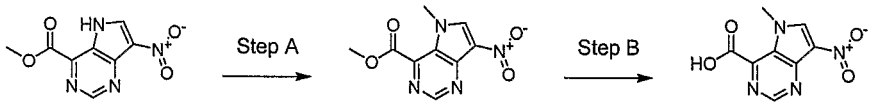
[0530] If one were to follow a similar procedure as described in Preparative Example 812, except using the amines indicated in Table I-29 below, and if one were to treat the obtained protected amines similarly as described in the Preparative Examples 813, the following compounds would be obtained.

Table I-29

Prep. Ex. #	amine	products
815		 AND

Prep. Ex. #	amine	products
816		
817		
818		
819		
820		
821		

Preparative Example 822



[0531] Step A

If one were to stir a mixture of the title compound from the Preparative Example 378, Step D, iodomethane and K_2CO_3 in DMF at room temperature overnight, concentrate the mixture and purify the residue by chromatography (silica), one would obtain the title compound.

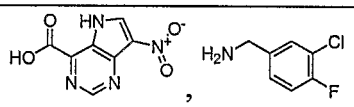
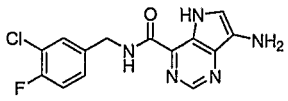
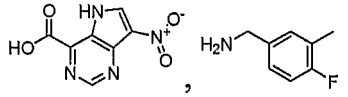
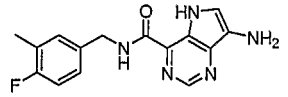
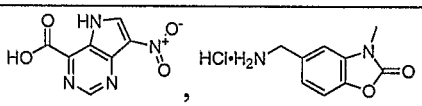
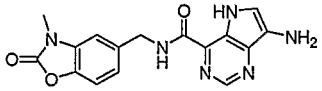
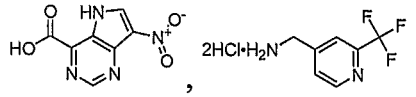
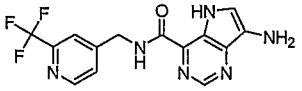
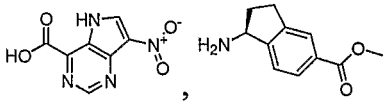
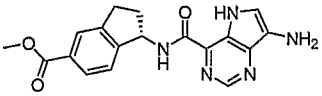
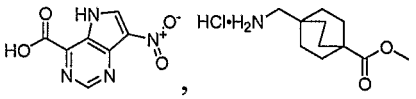
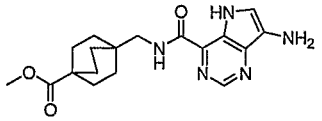
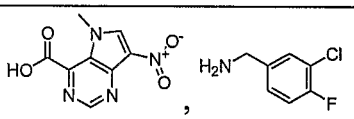
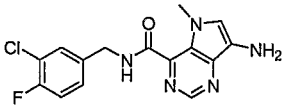
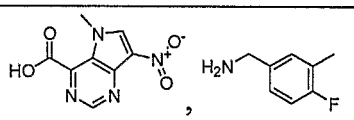
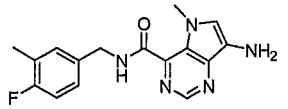
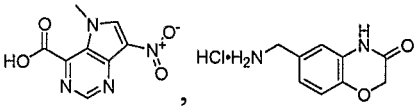
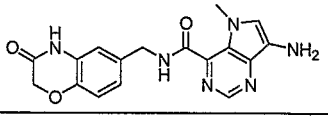
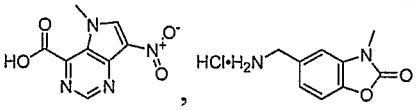
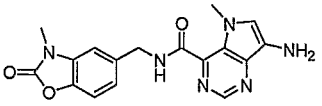
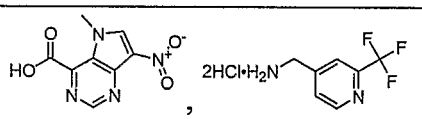
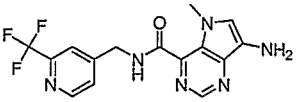
[0532] Step B

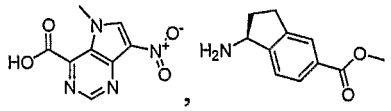
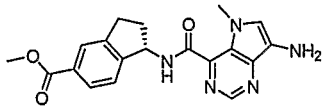
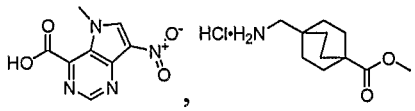
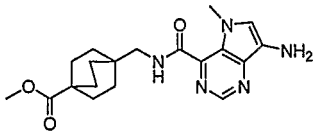
If one were to treat the title compound from Step A above similar as described in the Preparative Example 378, Step E, one would obtain the title compound.

Preparative Examples 823-835

[0533] If one were to follow a similar procedure as described in Preparative Example 379, except using the acids and amines indicated in Table I-30 below, the following compounds would be obtained.

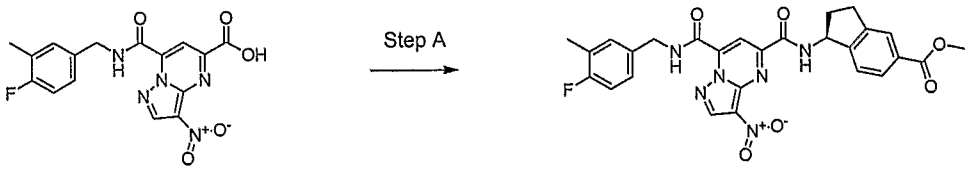
Table I-30

Prep. Ex. #	amine	product
823		
824		
825		
826		
827		
828		
829		
830		
831		
832		
833		

Prep. Ex. #	amine	product
834		
835		

Examples

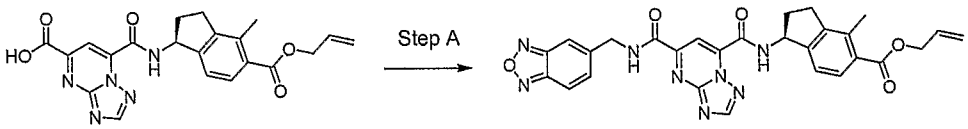
Example 1



[0534] Step A

To a solution of the title compound from the Preparative Example 335 (40 mg) in DMF (2 mL) were added the title compound from the Preparative Example 4, Step B (34 mg), PyBOP (84 mg) and $^{i}Pr_2NEt$ (46 μL). The mixture was stirred overnight, concentrated and purified by chromatography (silica, cyclohexane/EtOAc) to afford the title compound (23 mg, 40%). ^{1}H-NMR ($CDCl_3$) δ = 10.50 (br d, 1 H), 9.00 (s, 1 H), 8.85 (s, 1 H), 8.30 (br t, 1 H), 7.95 (s, 1 H), 7.90 (d, 2 H), 7.40 (d, 2 H), 7.25-7.10 (m, 2 H), 6.95 (m, 1 H), 5.80 (m, 1 H), 4.65 (d, 2 H), 3.90 (s, 3 H), 3.20-2.70 (m, 3 H), 2.25 (s, 3 H), 2.20-2.00 (m, 1 H).

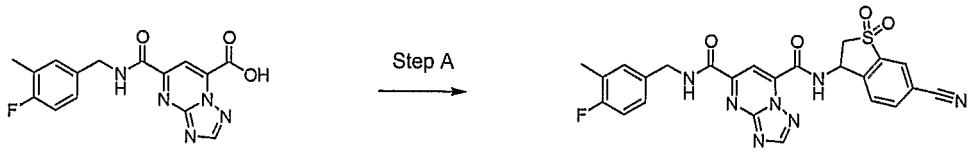
Example 2



[0535] Step A

To a solution of the title compound from the Preparative Example 373, Step A (30 mg) and the title compound from the Preparative Example 228, Step A (30 mg) in DMF (3 mL) were added *N*-methylmorpholine (40 μL), EDCI (25 mg) and HOAt (13 mg). The mixture was stirred overnight and then concentrated. The remaining residue was dissolved in EtOAc, washed with saturated $NaHCO_3$, 1N aqueous HCl and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a colorless solid (35 mg, 90%). $[MH]^+ = 553$.

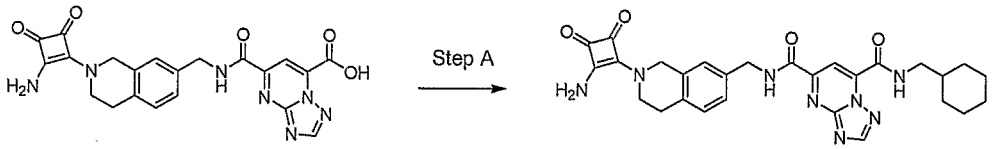
Example 3



[0536] Step A

To a solution of the title compound from the Preparative Example 331, Step A (31 mg) and the title compound from the Preparative Example 218, Step D (27 mg) in DMF (5 mL) were added *N*-methylmorpholine (13 μL), HATU (57 mg) and HOAt (16 mg). The mixture was stirred overnight and then concentrated. The remaining residue was dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$, 1N aqueous HCl and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a colorless solid (57 mg, >99%). $[MH]^+ = 520$.

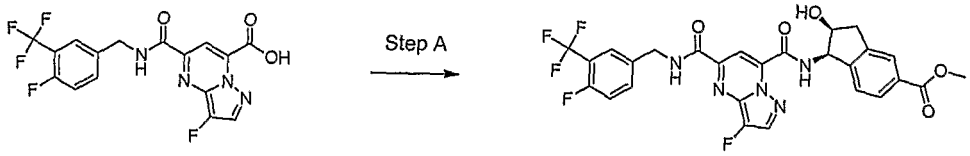
Example 4



[0537] Step A

To a solution of the title compound from the Preparative Example 349 (21.5 mg) in DMF (3 mL) were added cyclohexanemethylamine (30 μL), PyBrOP (29 mg) and HOAt (8 mg). The mixture was stirred over the weekend and then concentrated. The remaining residue was dissolved in $CHCl_3$, washed with saturated aqueous $NaHCO_3$, 1N aqueous HCl and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by preparative thin layer chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as an off-white solid (11.9 mg, 46%). $[MH]^+ = 543$.

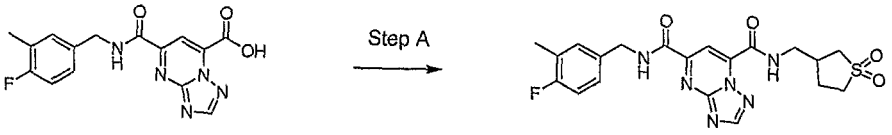
Example 5



[0538] Step A

To a mixture of the title compound from the Preparative Example 324, Step A (106 mg), DMF (20 mL) and CH_2Cl_2 (2.5 mL) at 0°C was added oxalyl chloride (116 μL). The ice bath was removed and the mixture was stirred for 45 min and concentrated. The resulting residue was brought up in CH_2Cl_2 (1.5 mL) and canulated into a mixture of the title compound from the Preparative Example 176, Step A (75 mg) and NEt_3 (122 μL) in CH_2Cl_2 (1 mL). The resulting mixture was stirred for 16 h and concentrated. The remaining solid was washed with MeOH (10 mL). The supernatant was concentrated and the resulting solid was washed with MeOH (10 mL). The yellow solids were combined to give the title compound (51 mg, 33%). $[M-H]^- = 588$.

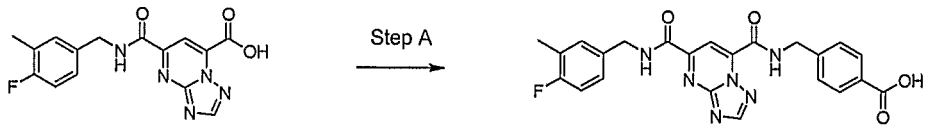
Example 6



[0539] Step A

To a mixture of *N*-cyclohexyl-carbodiimide-*N'*-methyl-polystyrene (43 mg) in DMF (100 μL) were added a 0.2M solution of the title compound from the Preparative Example 331, Step A in DMF (150 μL) and a 0.5M solution of HOBt in DMF (60 μL). The mixture was agitated for 30 min, then a 0.5M solution of (1,1-dioxidotetrahydrothien-3-yl)-methylamine in DMF (54 μL) was added and agitation at room temperature was continued for 12 h. The mixture was filtered, concentrated and dissolved in 1,2-dichloroethane (200 μL). (Polystyrylmethyl)-trimethylammonium bicarbonate (16 mg) was added and the mixture was agitated at room temperature for 2 h. Filtration and concentration afforded the title compound (13.1 mg, 95%). $[MH]^+ = 461$.

Example 7



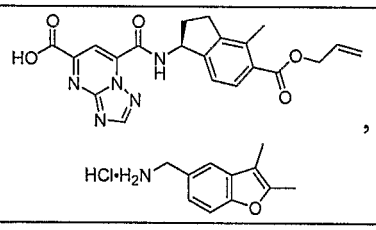
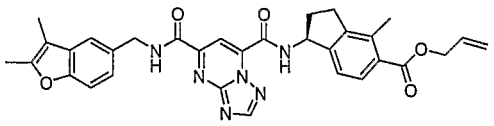
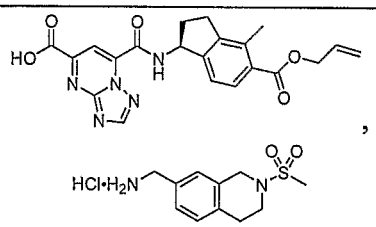
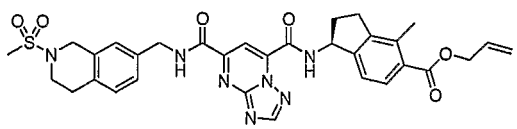
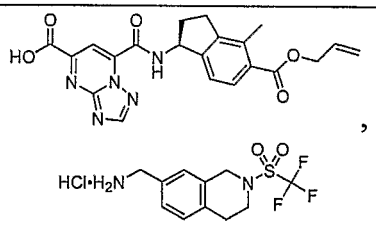
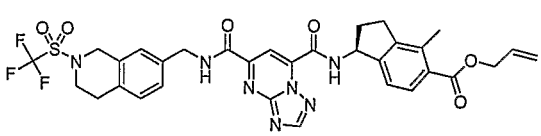
[0540] Step A

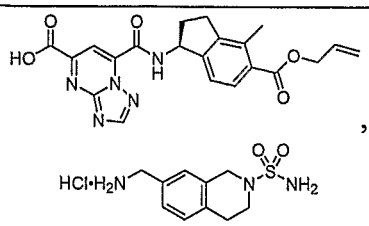
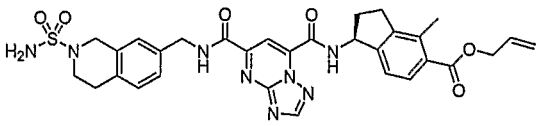
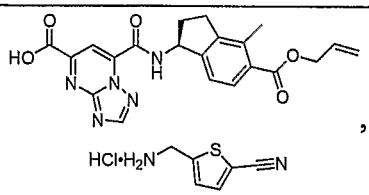
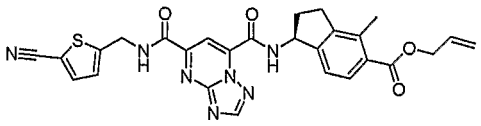
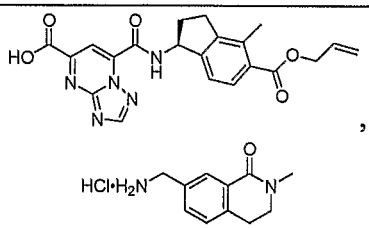
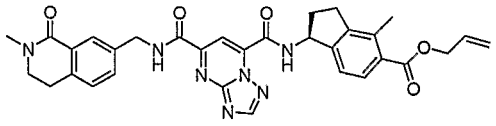
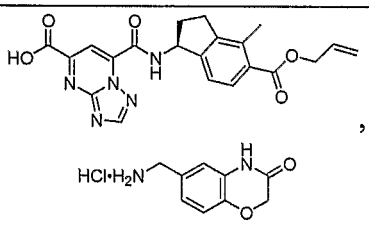
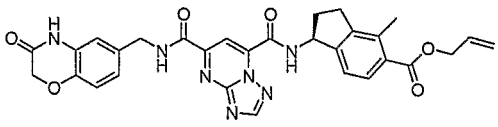
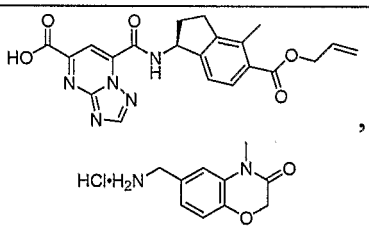
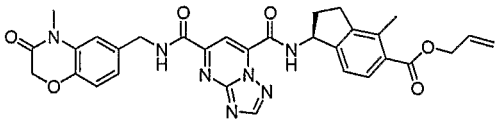
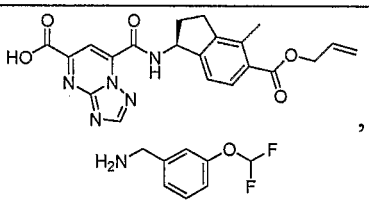
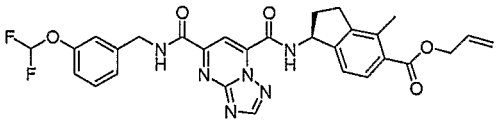
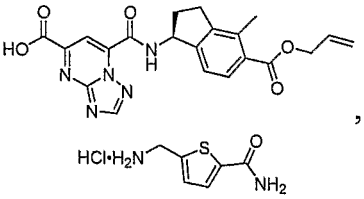
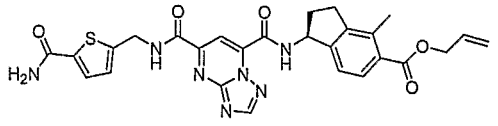
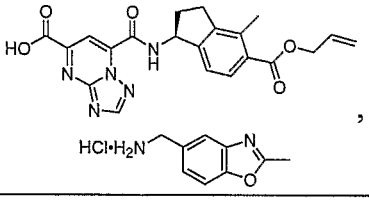
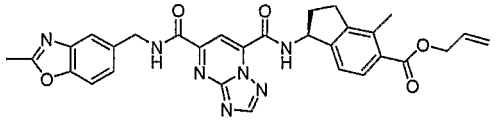
To a mixture of polystyrene-IIDQ (131 mg) in DMF (800 μL) were added the title compound from the Preparative Example 331, Step A (39 mg) and a 0.5M solution of commercially available 4-aminomethyl-benzoic acid (40 mg). The mixture was agitated for 24 h, filtered and concentrated to afford the title compound (40 mg, 73%). $[MH]^+ = 463$.

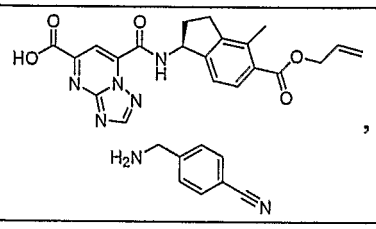
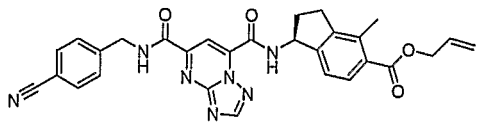
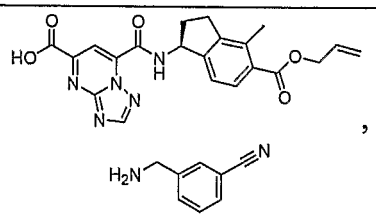
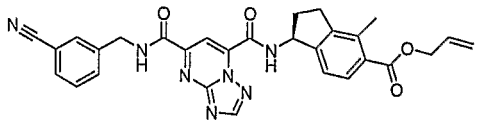
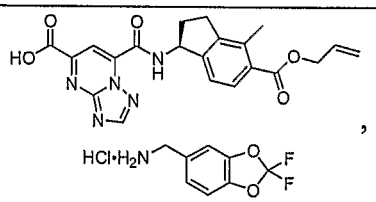
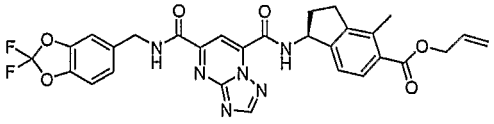
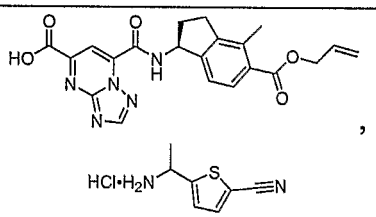
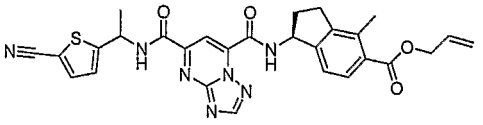
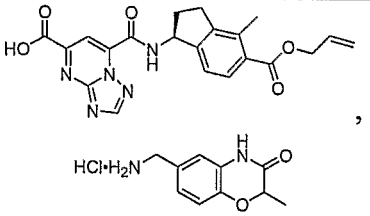
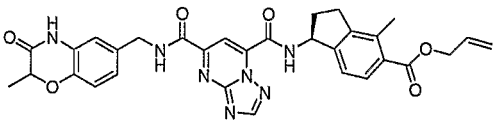
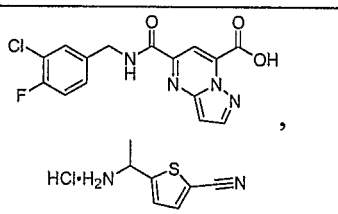
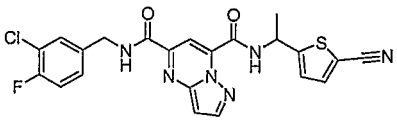
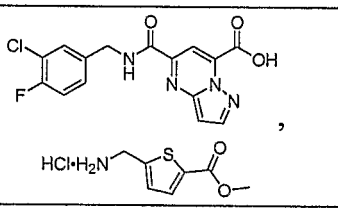
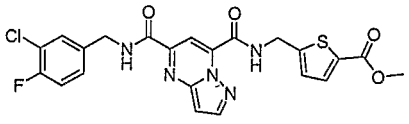
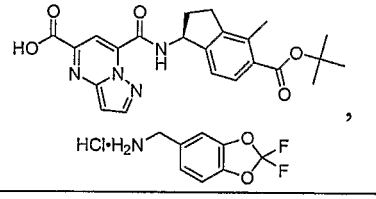
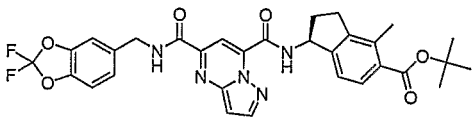
Examples 8-277

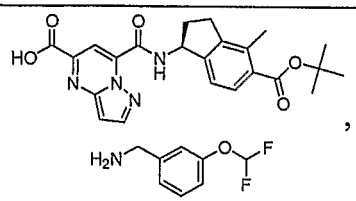
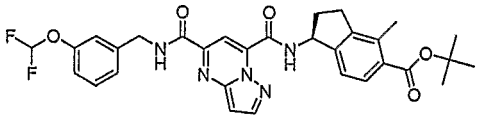
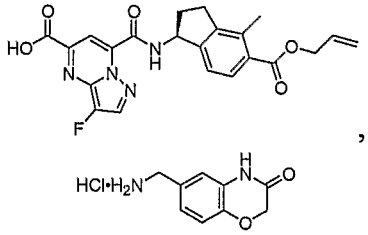
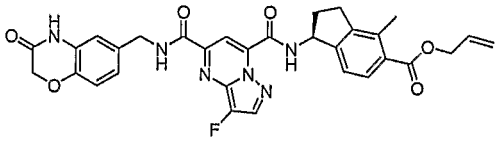
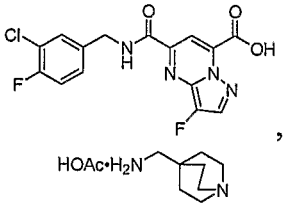
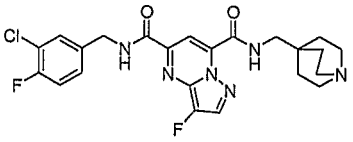
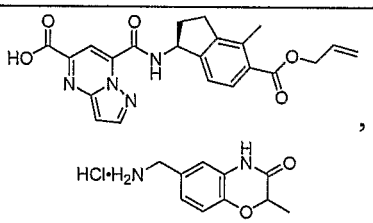
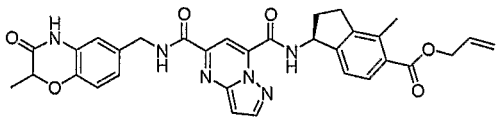
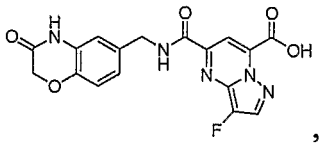
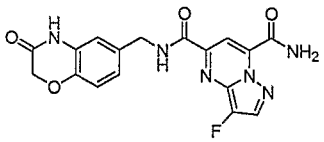
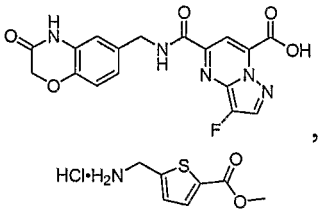
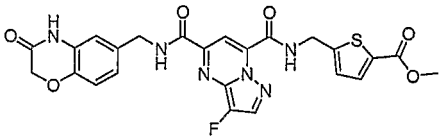
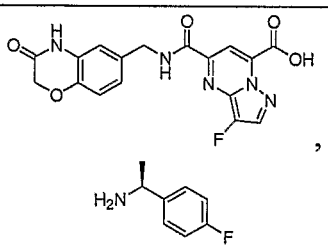
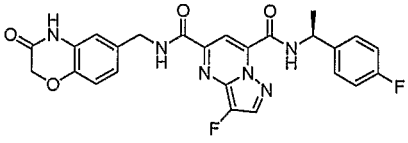
[0541] Following similar procedures as described in the Examples 1 (method A), 2 (method B), 3 (method C), 4 (method D), 5 (method E), 6 (method F) or 7 (method G), except using the acids and amines indicated in Table II-1 below, the following compounds were prepared.

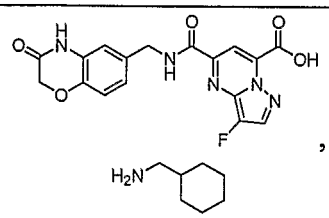
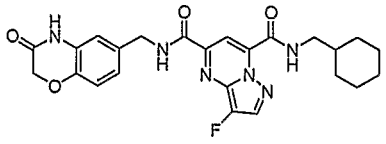
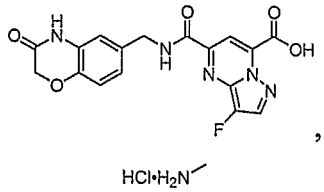
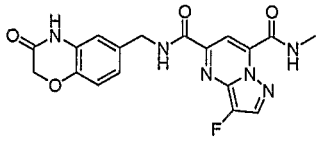
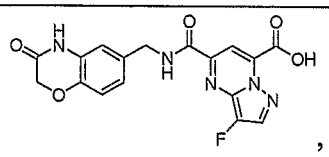
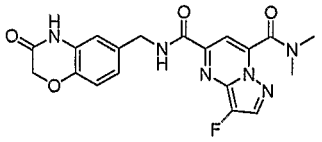
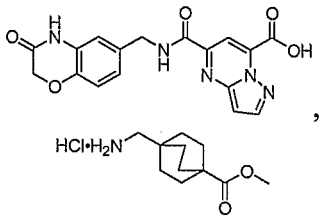
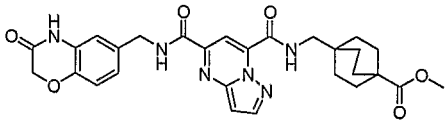
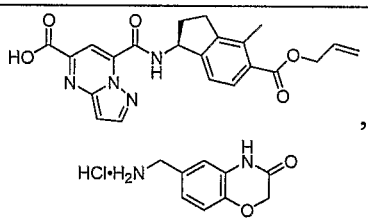
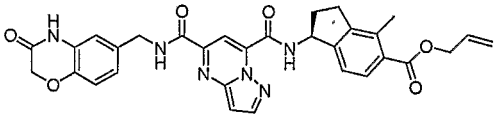
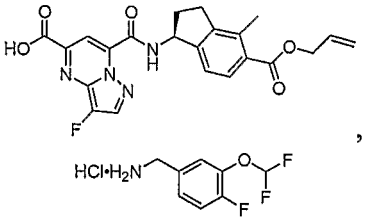
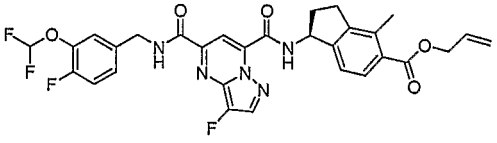
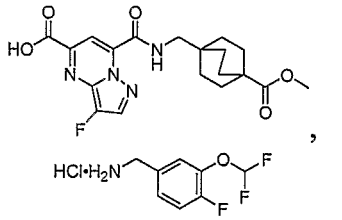
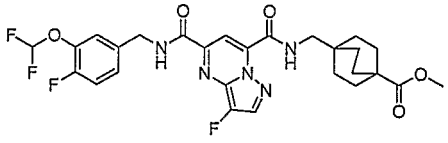
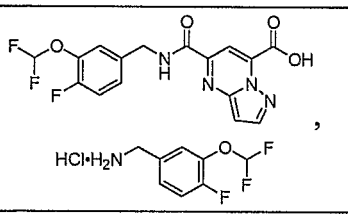
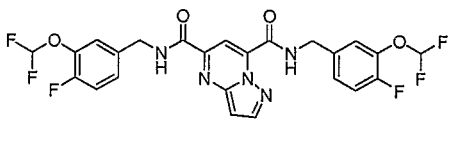
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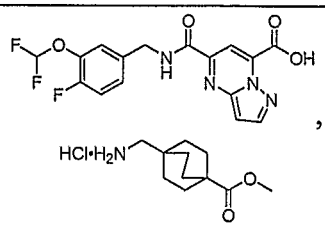
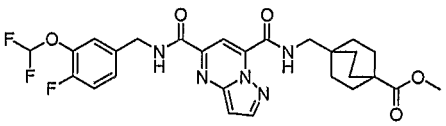
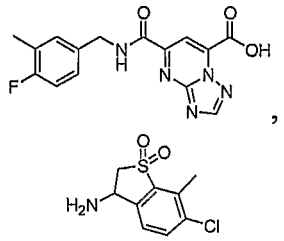
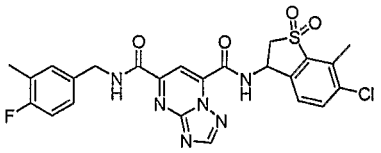
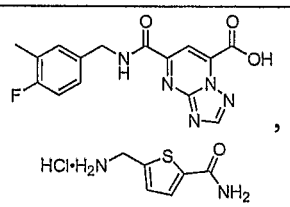
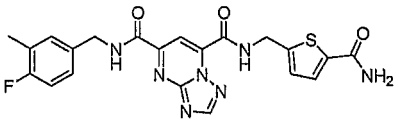
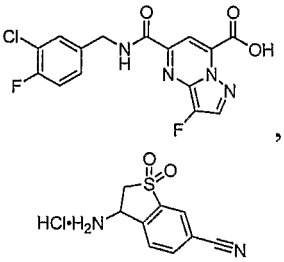
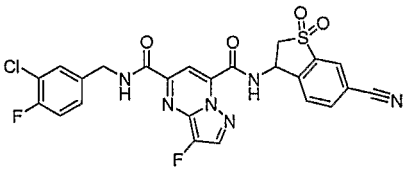
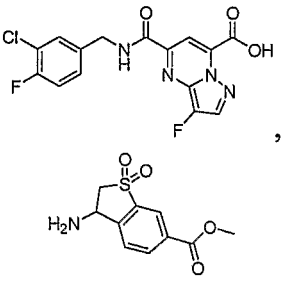
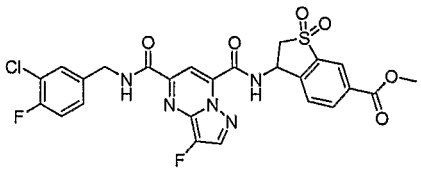
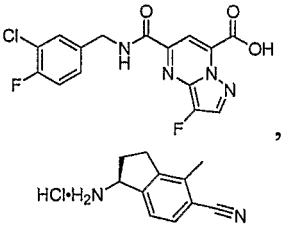
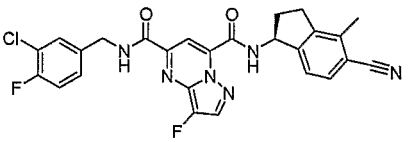
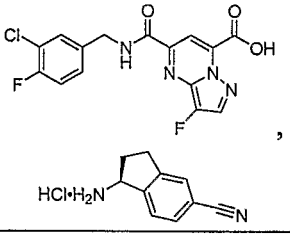
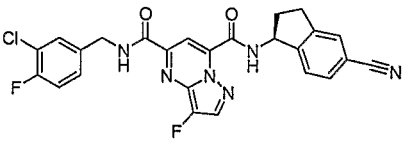
Ex. #	acid, amine	product	method, yield
8			B, 90% $[MH]^+ = 579$
9			B, 80% $[MH]^+ = 644$
10			B, 86% $[MH]^+ = 698$

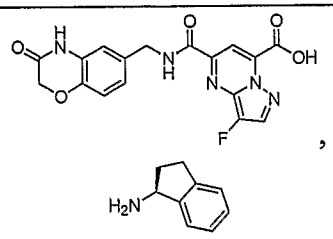
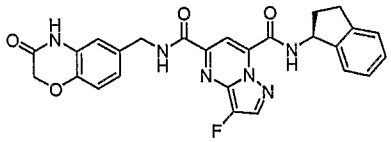
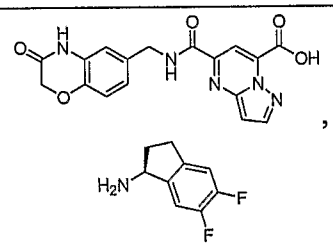
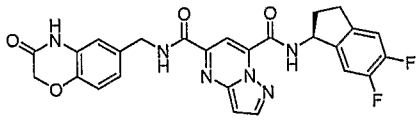
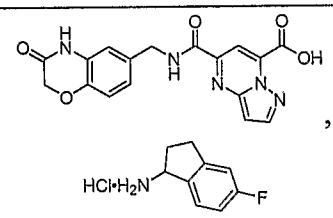
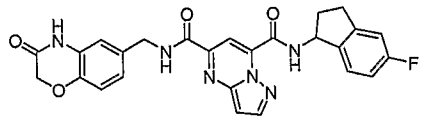
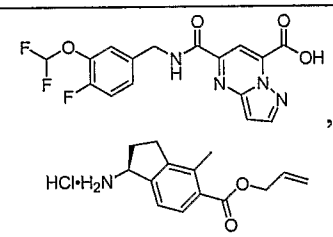
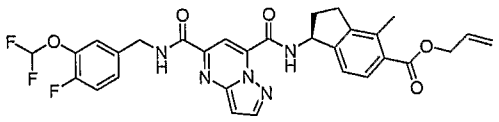
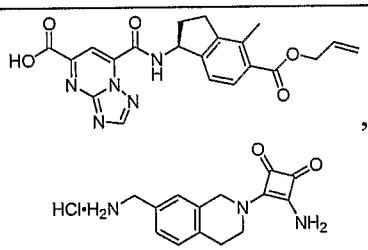
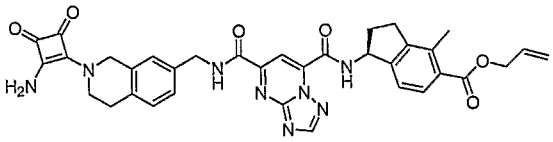
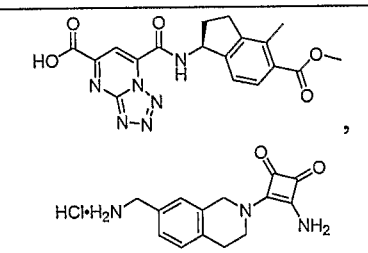
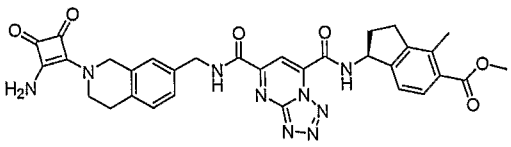
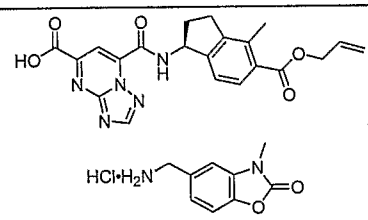
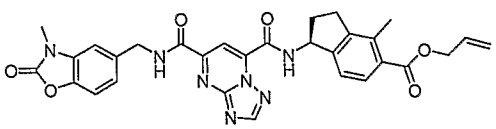
Ex. #	acid, amine	product	method, yield
11			B, >99% $[MH]^+ = 645$
12			B, 98% $[MH]^+ = 542$
13			B, >99% $[MH]^+ = 594$
14			B, 95% $[MH]^+ = 582$
15			B, >99% $[MH]^+ = 596$
16			B, n.d. $[MH]^+ = 577$
17			B, n.d. $[MH]^+ = 560$
18			B, n.d. $[MH]^+ = 566$

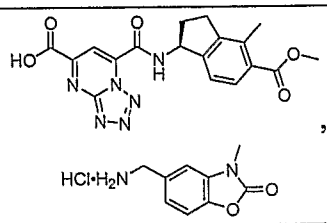
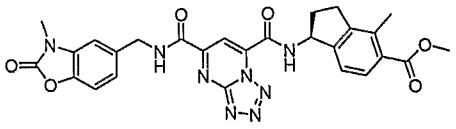
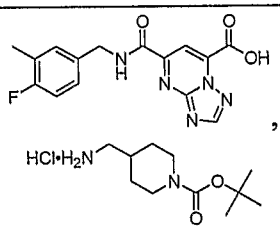
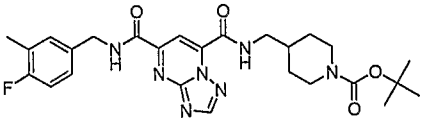
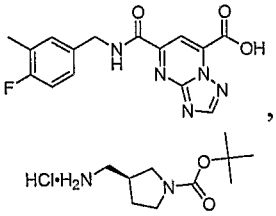
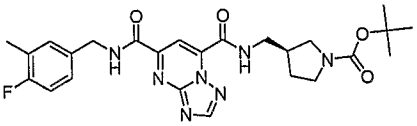
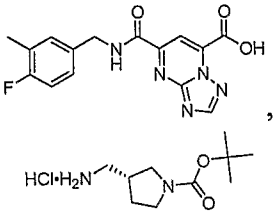
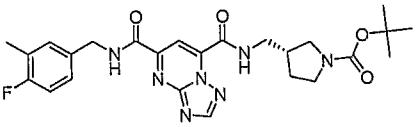
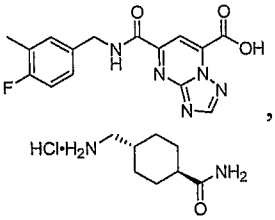
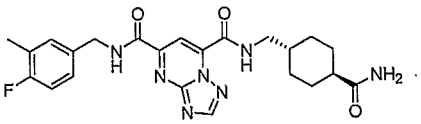
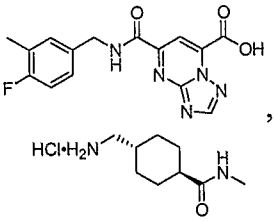
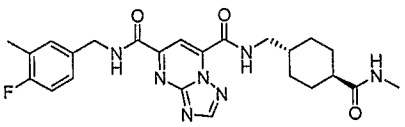
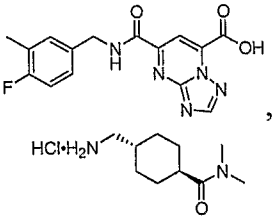
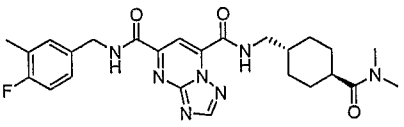
Ex. #	acid, amine	product	method, yield
19			B, n.d. $[MH]^+ = 536$
20			B, n.d. $[MH]^+ = 536$
21			B, n.d. $[MH]^+ = 591$
22			B, n.d. $[MH]^+ = 556$
23			B, n.d. $[MH]^+ = 596$
24			B, 92% $[MH]^+ = 483$
25			B, 85% $[MH]^+ = 502$
26			B, 79% $[MH]^+ = 606$

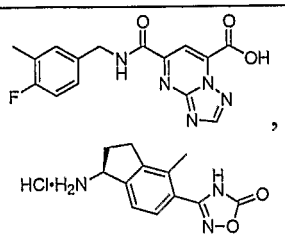
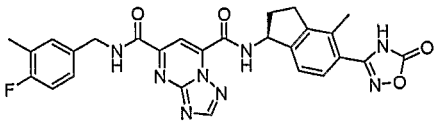
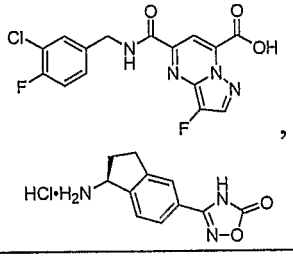
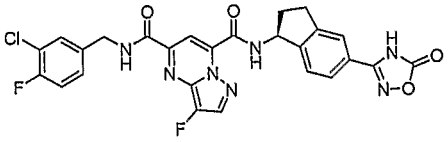
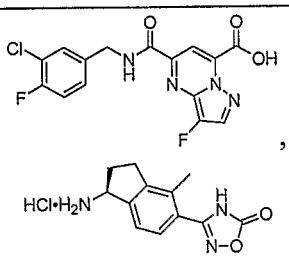
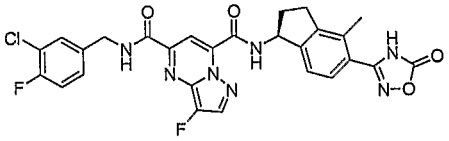
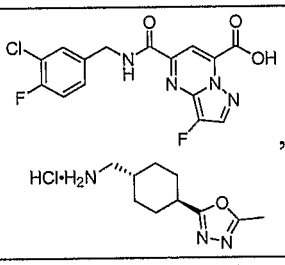
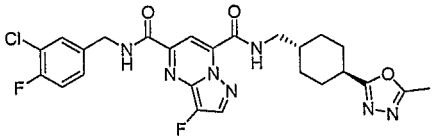
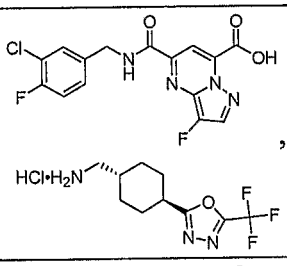
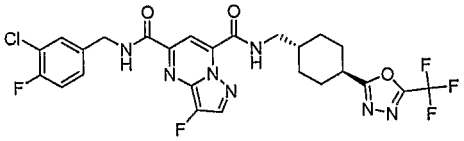
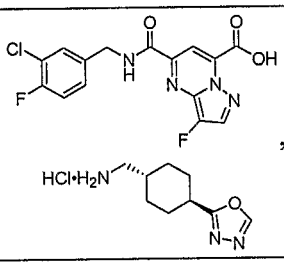
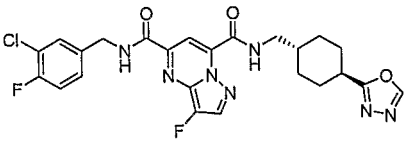
Ex. #	acid, amine	product	method, yield
27			B, 88% $[MH]^+ = 592$
28			B, 95% $[MH]^+ = 599$
29			B, 18% $[MH]^+ = 489$
30			B, 95% $[MH]^+ = 595$
31	 0.5M NH_3 in 1,4-dioxane		B, 41% $[MH]^+ = 385$
32			B, 87% $[MH]^+ = 539$
33			B, 45% $[MH]^+ = 507$

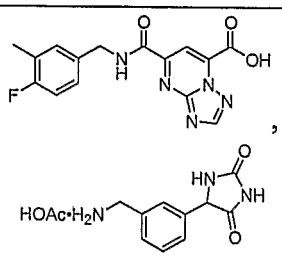
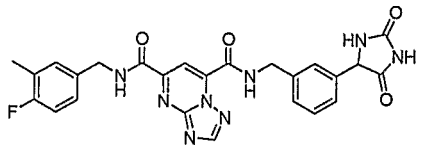
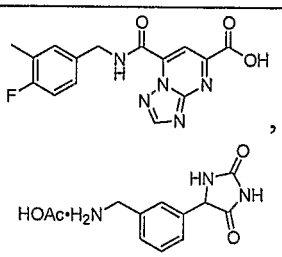
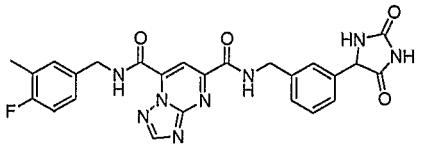
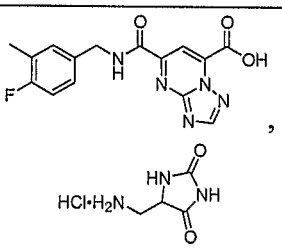
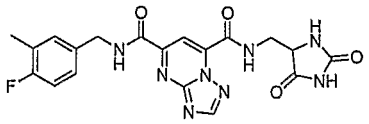
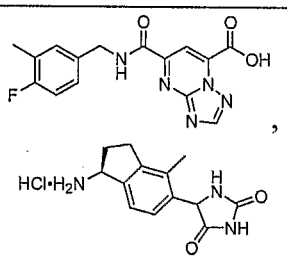
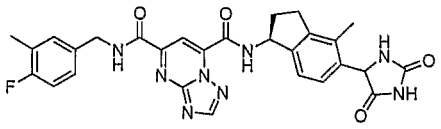
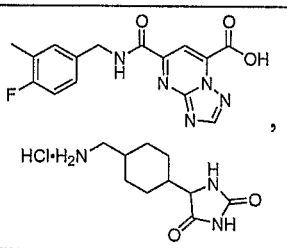
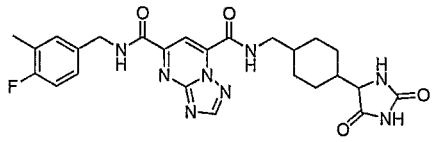
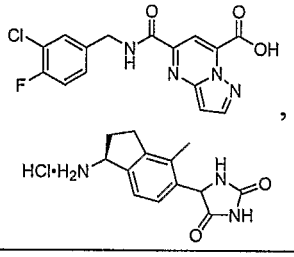
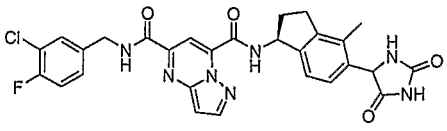
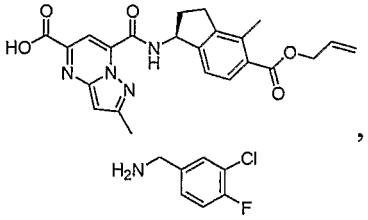
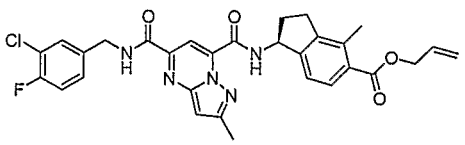
Ex. #	acid, amine	product	method, yield
34			B, 77% $[MH]^+ = 481$
35			B, 65% $[MH]^+ = 399$
36	 2M Me_2NH in THF		B, 35% $[MH]^+ = 413$
37			B, 97% $[MH]^+ = 547$
38			B, 84% $[MH]^+ = 581$
39			B, 81% $[MH]^+ = 612$
40			B, 85% $[MH]^+ = 578$
41			B, n.d.% $[MH]^+ = 554$

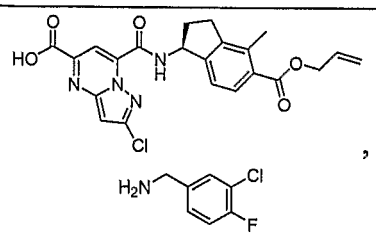
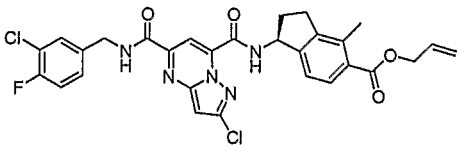
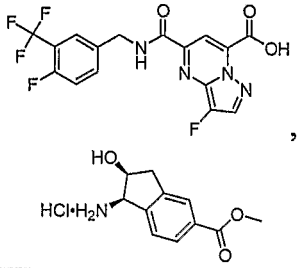
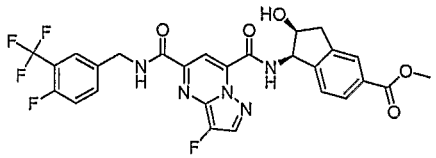
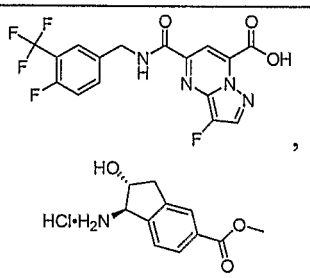
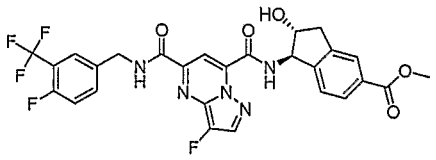
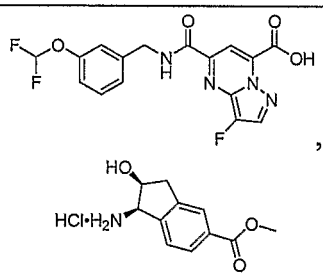
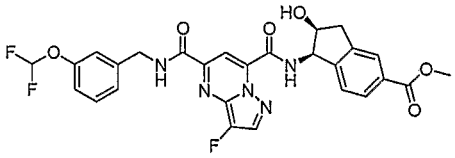
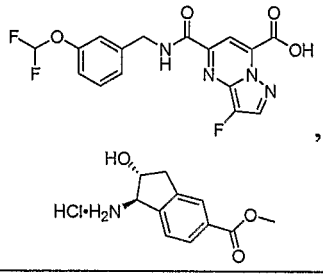
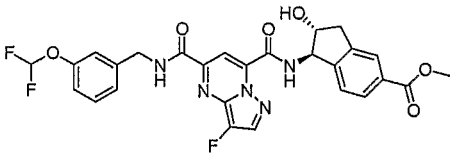
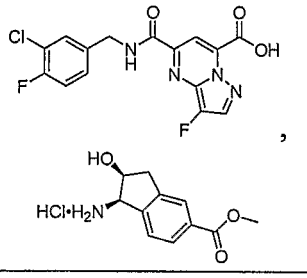
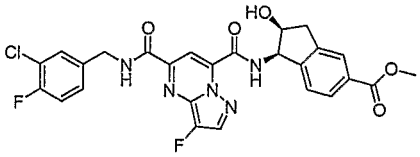
Ex. #	acid, amine	product	method, yield
42			B, 68% $[MH]^+ = 560$
43			C, 95% $[MH]^+ = 543$
44			C, 56% $[MH]^+ = 468$
45			D, >99% $[MH]^+ = 557$
46			D, 47% $[MH]^+ = 590$
47			D, >99% $[MH]^+ = 521$
48			D, >99% $[MH]^+ = 507$

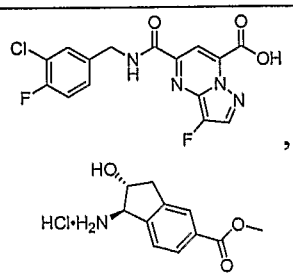
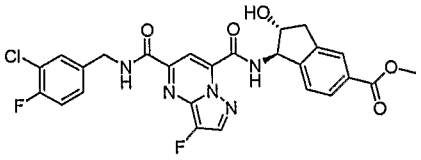
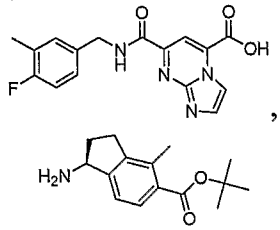
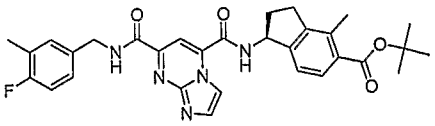
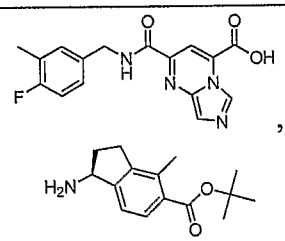
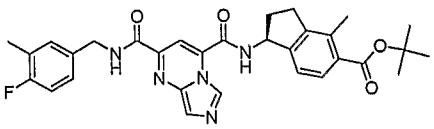
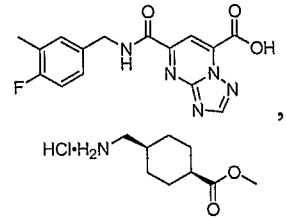
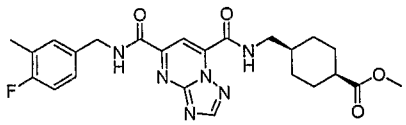
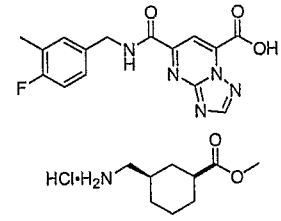
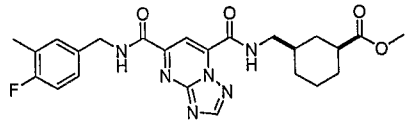
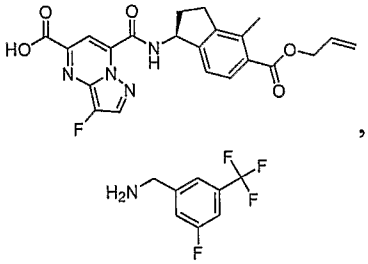
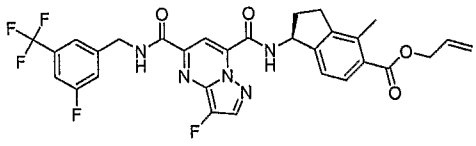
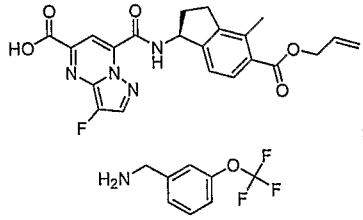
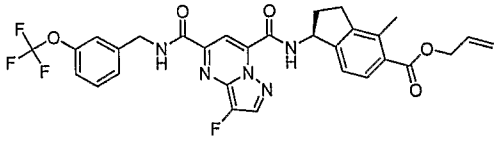
Ex. #	acid, amine	product	method, yield
49			D, 76% $[MH]^+ = 501$
50			D, >99% $[MH]^+ = 519$
51			D, 30% $[MH]^+ = 501$
52			D, 77% $[MH]^+ = 594$
53			C, 62% $[MNa]^+ = 661$
54			C, 76% $[MH]^+ = 636$
55			C, 85% $[MH]^+ = 582$

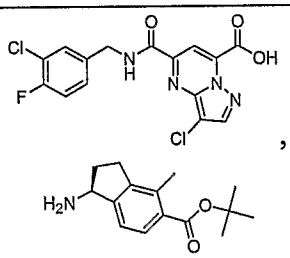
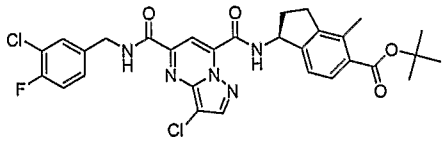
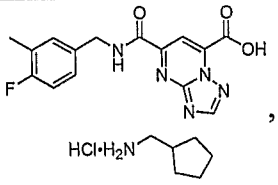
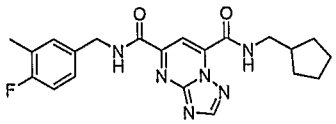
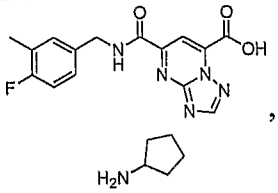
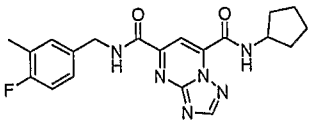
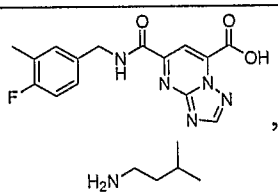
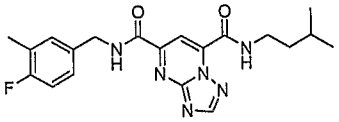
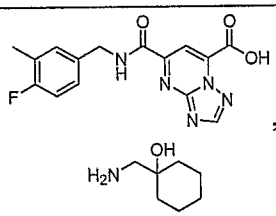
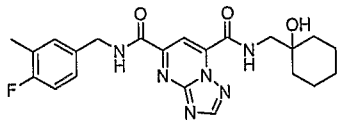
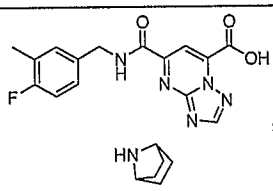
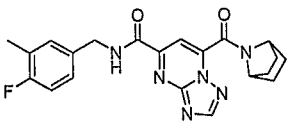
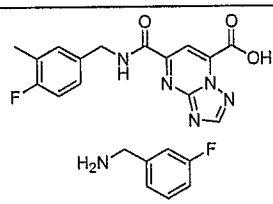
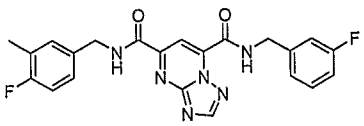
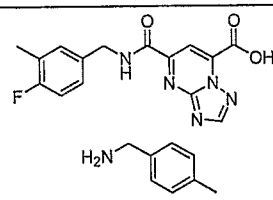
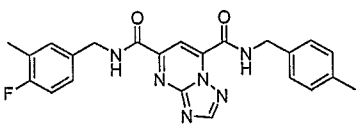
Ex. #	acid, amine	product	method, yield
56			C, 77% $[MH]^+ = 557$
57			C, 91% $[MNa]^+ = 562$
58			C, 85% $[M\text{-}Boc]^+ = 412$
59			C, 98% $[M\text{-}Boc]^+ = 412$
60			C, 92% $[MH]^+ = 468$
61			C, 71% $[MH]^+ = 482$
62			C, 86% $[MH]^+ = 496$

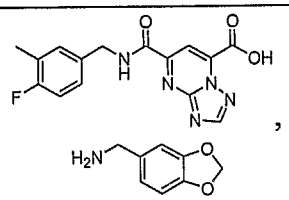
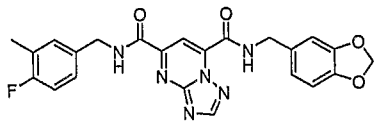
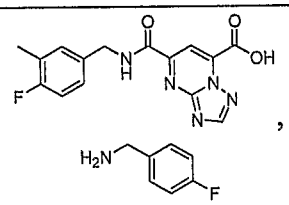
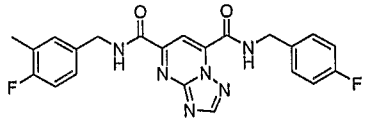
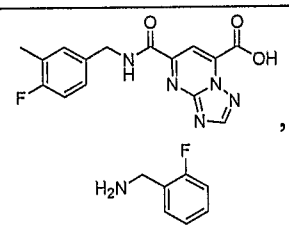
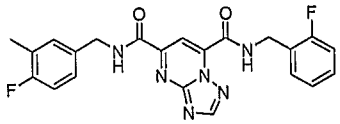
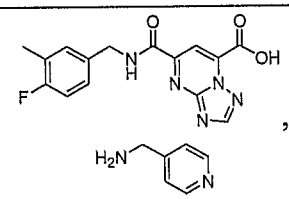
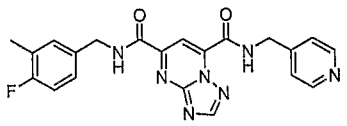
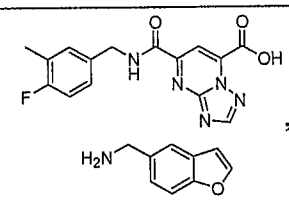
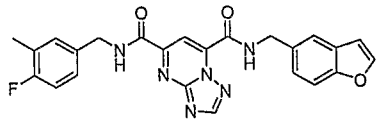
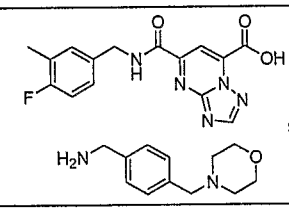
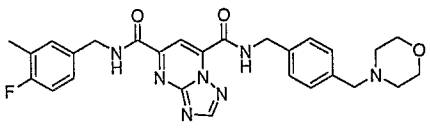
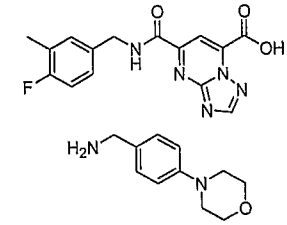
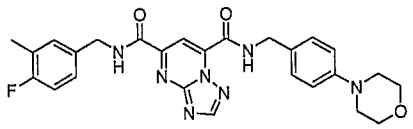
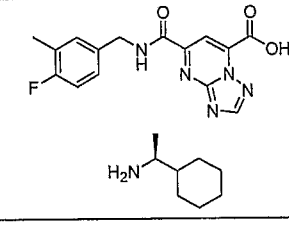
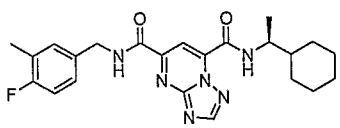
Ex. #	acid, amine	product	method, yield
63			C, 75% $[MH]^+ = 483$
64			C, 81% $[MH]^+ = 566$
65			C, 97% $[MH]^+ = 580$
66			C, 87% $[MH]^+ = 544$
67			C, 88% $[MH]^+ = 598$
68			C, 71% $[MH]^+ = 530$

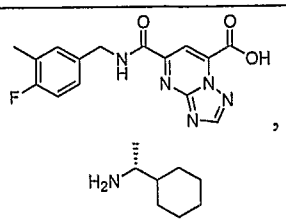
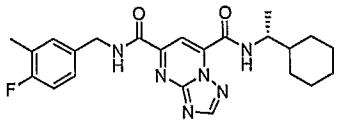
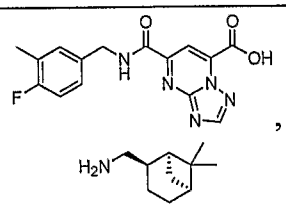
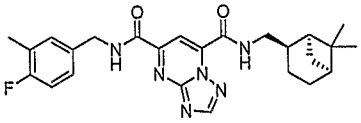
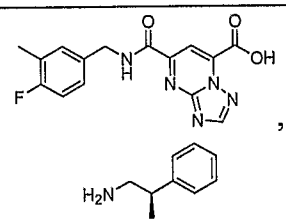
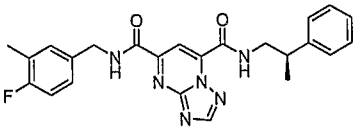
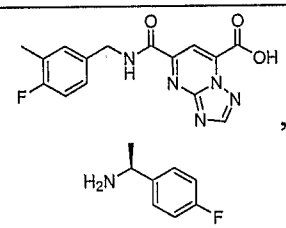
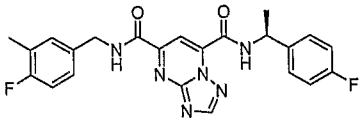
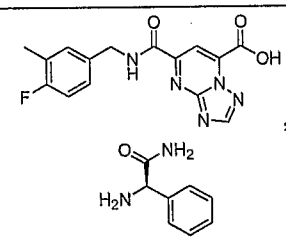
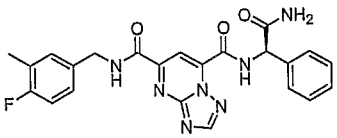
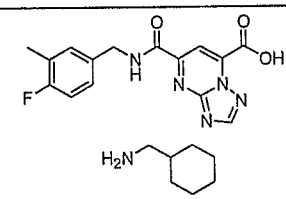
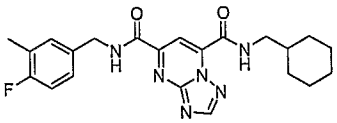
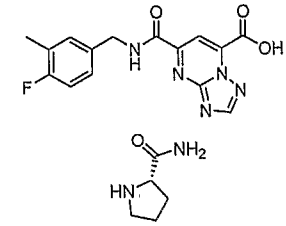
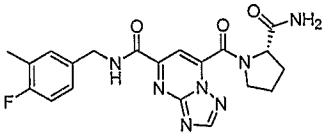
Ex. #	acid, amine	product	method, yield
69			E, 23% $[MH]^+ = 517$
70			E, 39% $[MH]^+ = 517$
71			E, 82% $[MH]^+ = 441$
72			E, 59% $[MH]^+ = 557$
73			E, 21% $[MH]^+ = 523$
74			E, 73% $[MH]^+ = 576$
75			E, 73% $[MH]^+ = 576$

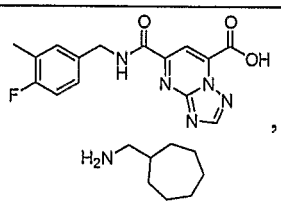
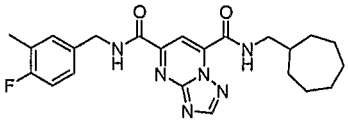
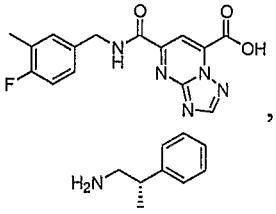
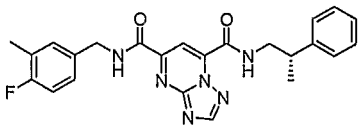
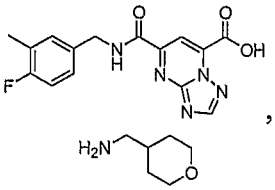
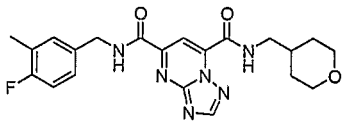
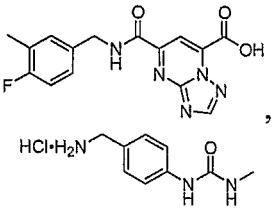
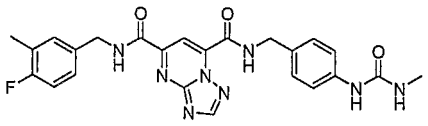
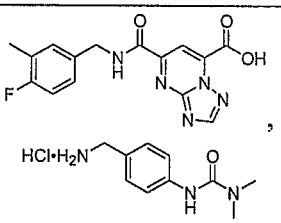
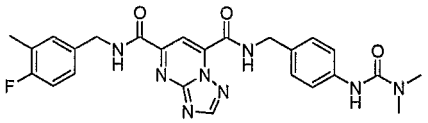
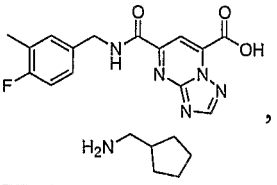
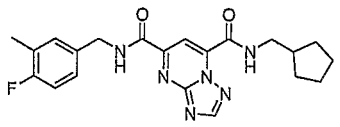
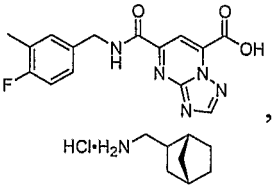
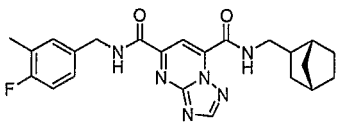
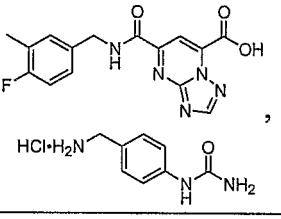
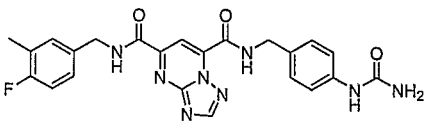
Ex. #	acid, amine	product	method, yield
76			E, 38% $[MH]^+ = 596$
77			E, 33% $[M-H]^- = 588$
78			E, 40% $[M-H]^- = 588$
79			E, 30% $[M-H]^- = 568$
80			E, 42% $[M-H]^- = 568$
81			E, 42% $[M-H]^- = 588$

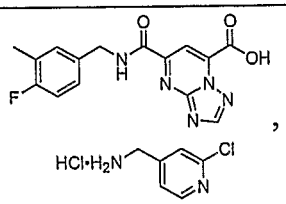
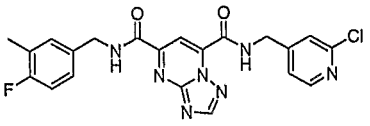
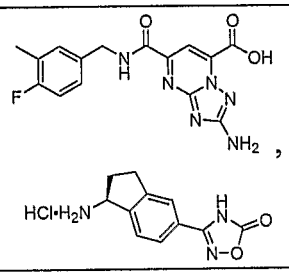
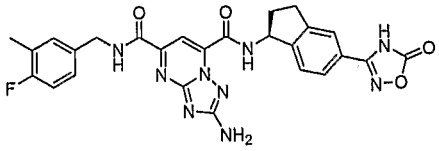
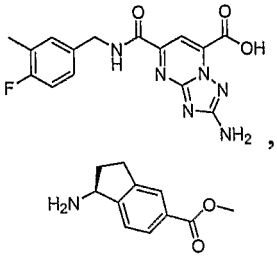
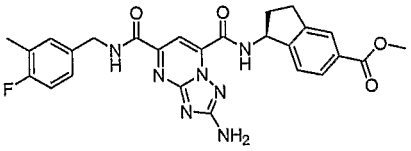
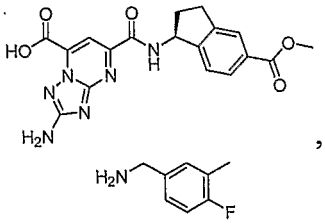
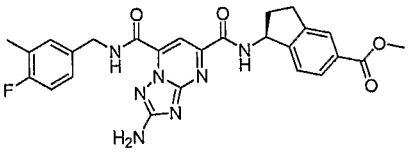
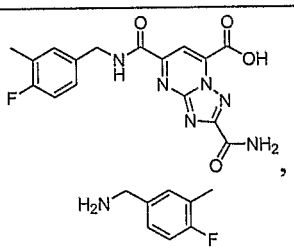
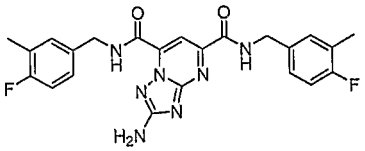
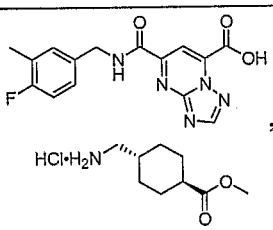
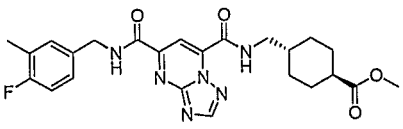
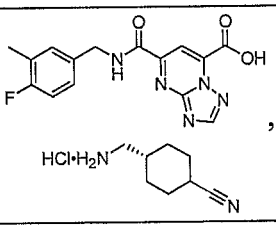
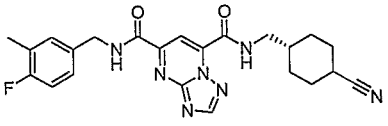
Ex. #	acid, amine	product	method, yield
82			E, 26% $[M-H]^-$ = 554
83			E, 60% (over 2 steps), $[M-H]^-$ = 556
84			E, 11% (over 2 steps), $[M-H]^-$ = 556
85			C, 77% $[MH]^+$ = 483
86			C, 66% $[MH]^+$ = 483
87			C, >99% $[MH]^+$ = 614
88			C, >99% $[MH]^+$ = 612

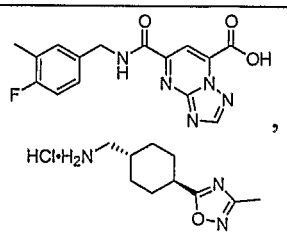
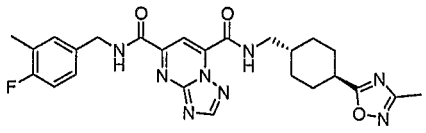
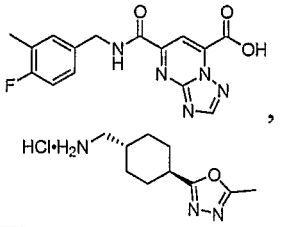
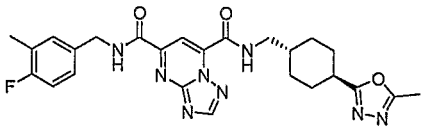
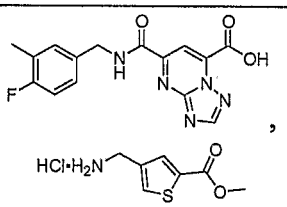
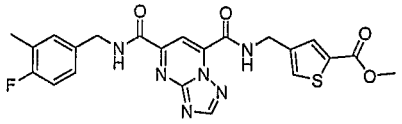
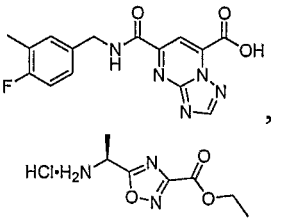
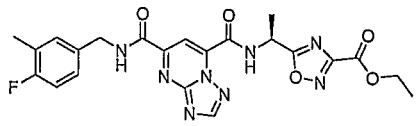
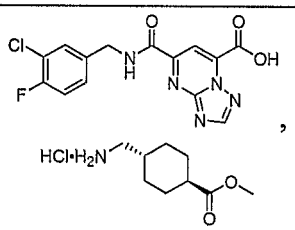
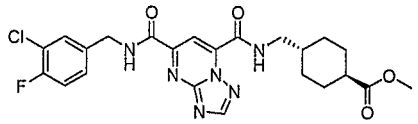
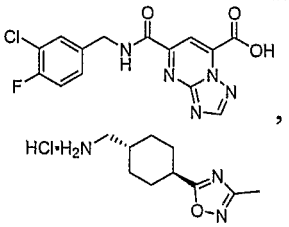
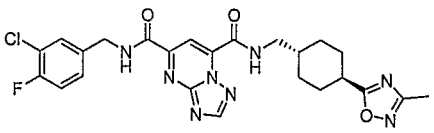
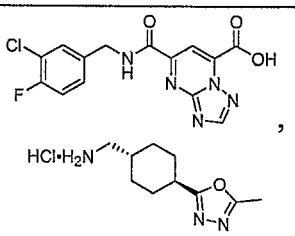
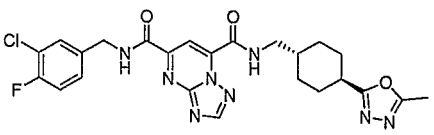
Ex. #	acid, amine	product	method, yield
89			C, 48% $[MNa]^+ = 634$
90			C, 54% $[MH]^+ = 410$
91			F, 87% $[MH]^+ = 397$
92			F, >99% $[MH]^+ = 399$
93			F, 61% $[MH]^+ = 441$
94			F, 67% $[MH]^+ = 409$
95			F, 40% $[MH]^+ = 437$
96			F, 36% $[MH]^+ = 433$

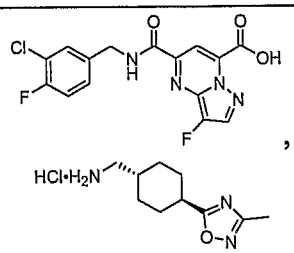
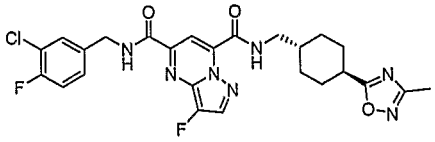
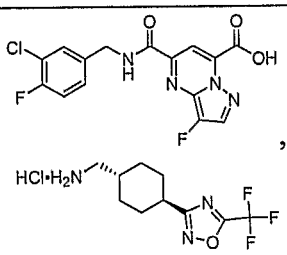
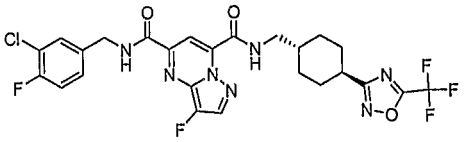
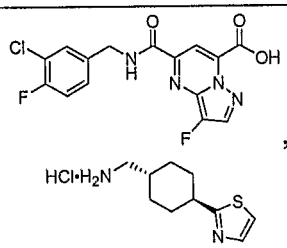
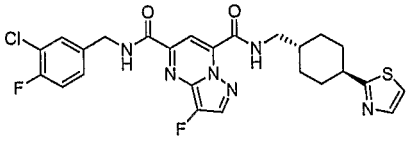
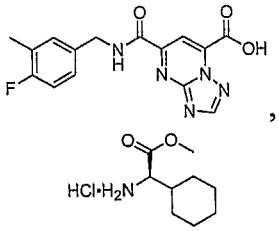
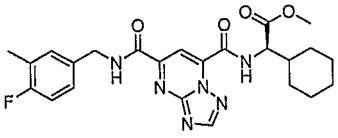
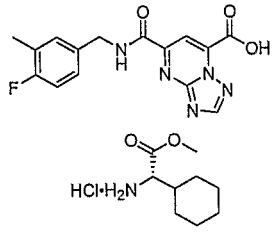
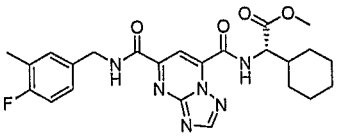
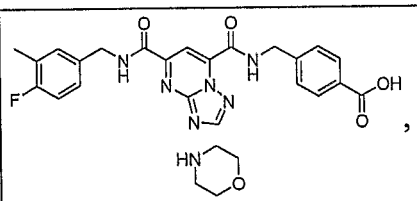
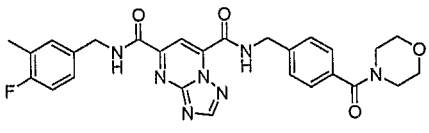
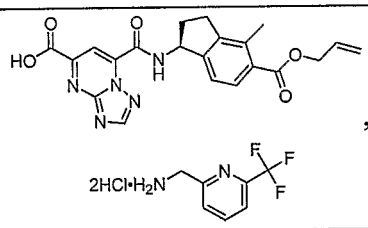
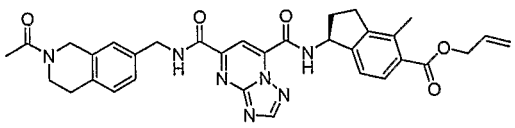
Ex. #	acid, amine	product	method, yield
97			F, 54% $[MH]^+ = 463$
98			F, 52% $[MH]^+ = 437$
99			F, 48% $[MH]^+ = 437$
100			F, 51% $[MH]^+ = 420$
101			F, 56% $[MH]^+ = 459$
102			F, 56% $[MH]^+ = 518$
103			F, 23% $[MH]^+ = 504$
104			F, 68% $[MH]^+ = 439$

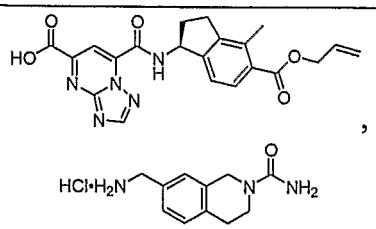
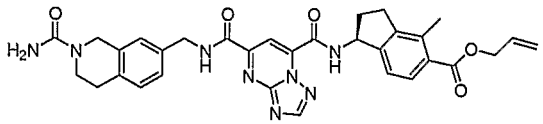
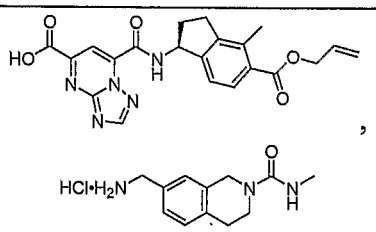
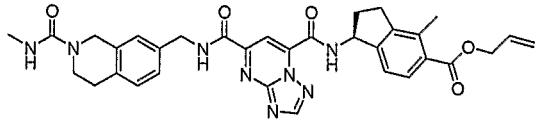
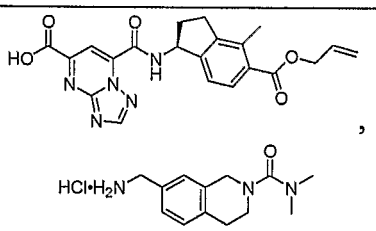
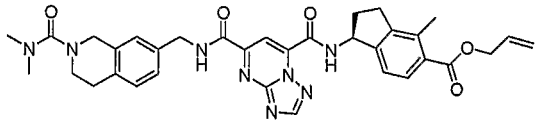
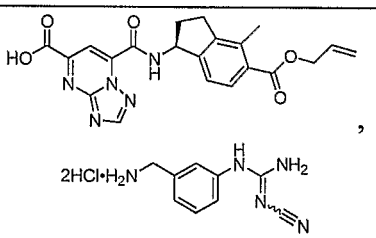
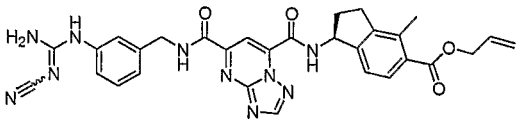
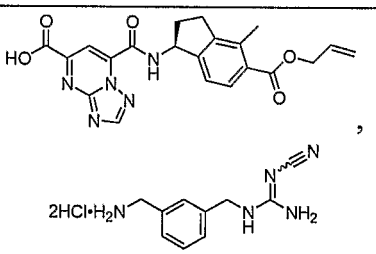
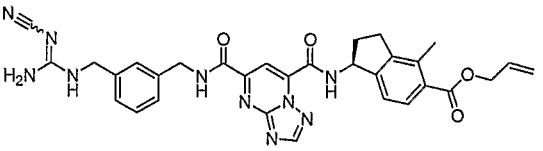
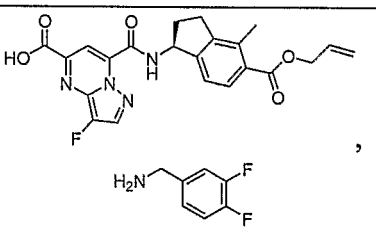
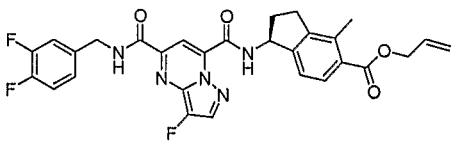
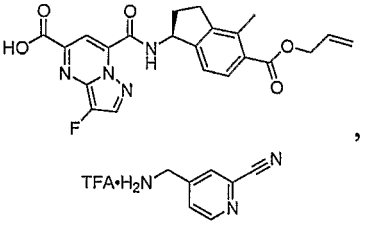
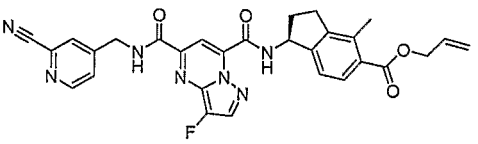
Ex. #	acid, amine	product	method, yield
105			F, 56% $[MH]^+ = 439$
106			F, 95% $[MH]^+ = 465$
107			F, 93% $[MH]^+ = 447$
108			G, 87% $[MH]^+ = 451$
109			G, >99% $[MH]^+ = 462$
110			G, 99% $[MH]^+ = 425$
111			G, 85% $[MH]^+ = 426$

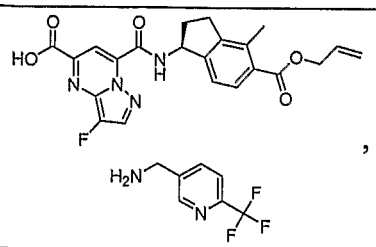
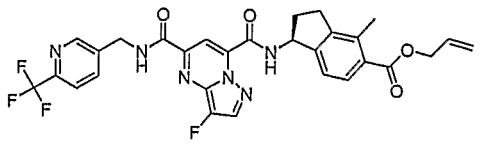
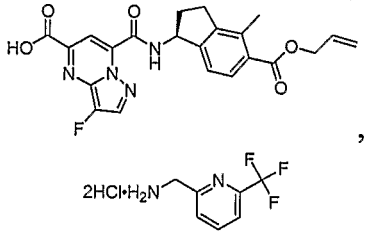
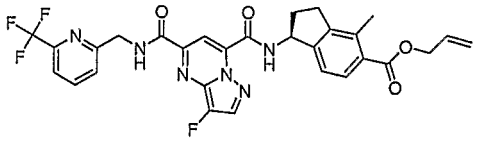
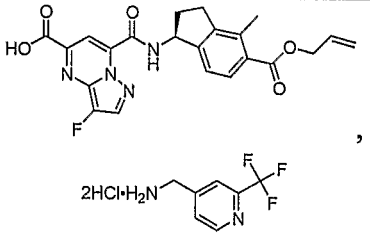
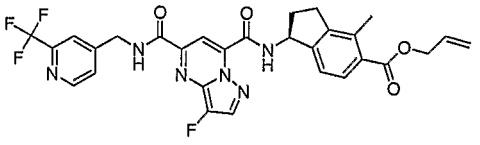
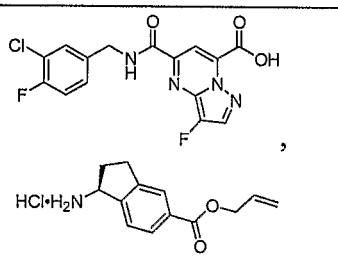
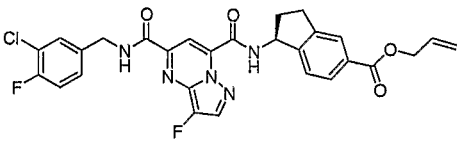
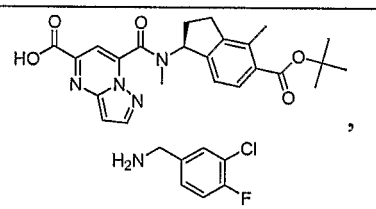
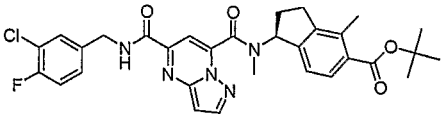
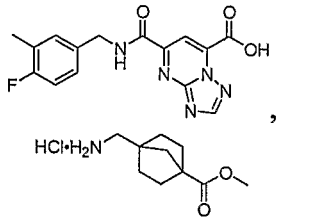
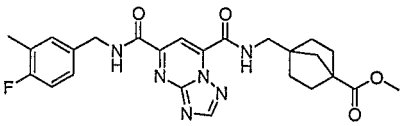
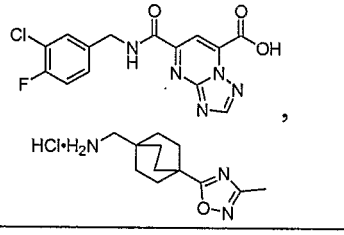
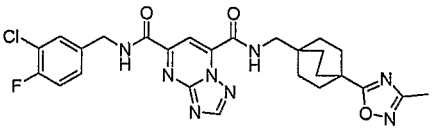
Ex. #	acid, amine	product	method, yield
112			F, 64% $[MH]^+ = 439$
113			F, 97% $[MH]^+ = 447$
114			G, 94% $[MH]^+ = 427$
115			G, 26% $[MH]^+ = 491$
116			G, 40% $[MH]^+ = 505$
117			C, 54% $[MH]^+ = 411$
118			C, 86% $[MH]^+ = 437$
119			C, 21% $[MH]^+ = 477$

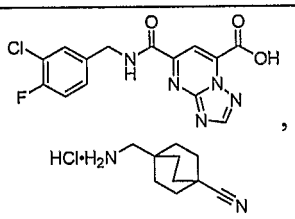
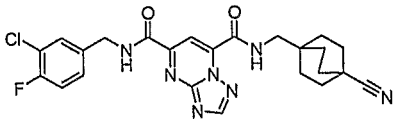
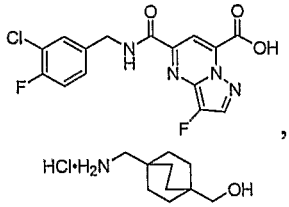
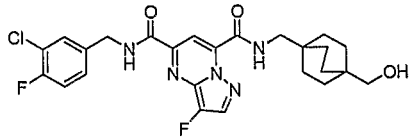
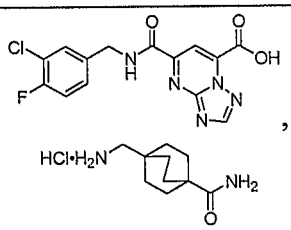
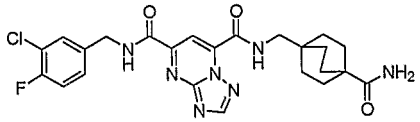
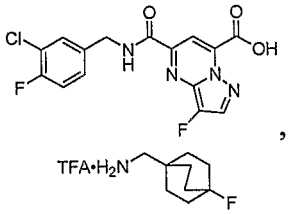
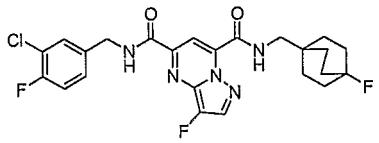
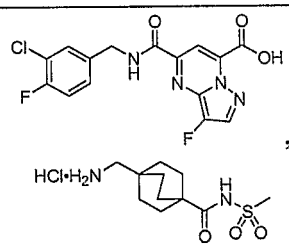
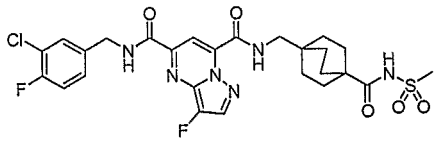
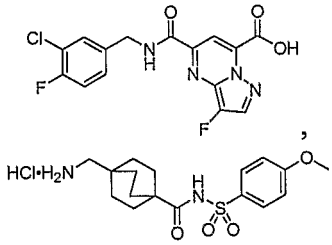
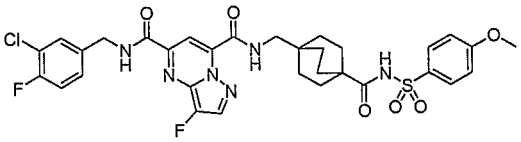
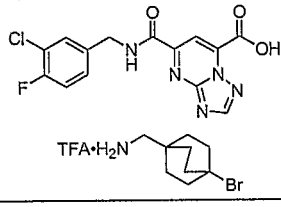
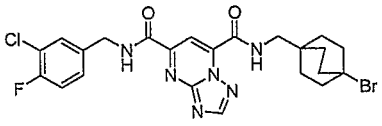
Ex. #	acid, amine	product	method, yield
120			C, 57% $[MH]^+ = 454$
121			C, 31% $[MH]^+ = 544$
122			C, 66% $[MH]^+ = 518$
123			C, 26% $[MH]^+ = 518$
124			C, 14% $[MH]^+ = 494$
125			C, 41% $[MH]^+ = 483$
126			C, 75% $[MH]^+ = 450$

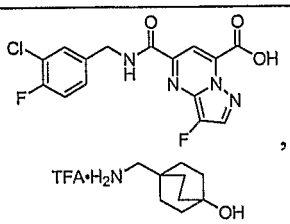
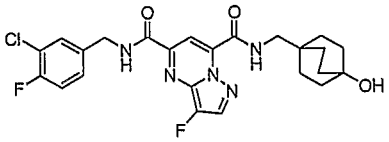
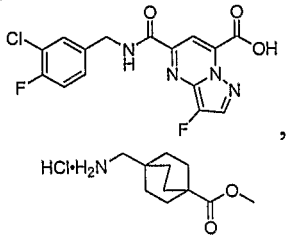
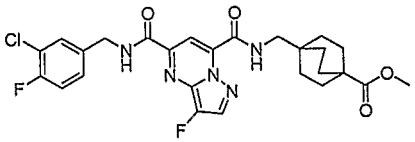
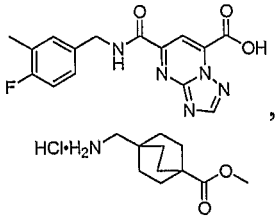
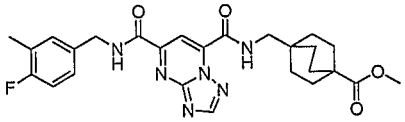
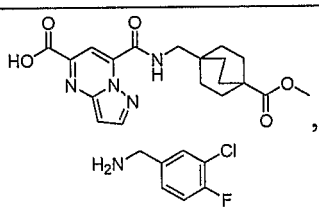
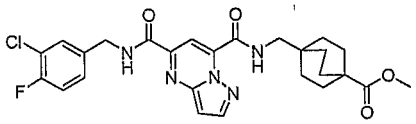
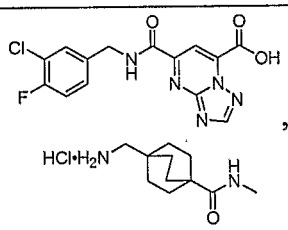
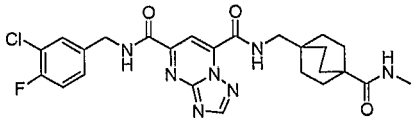
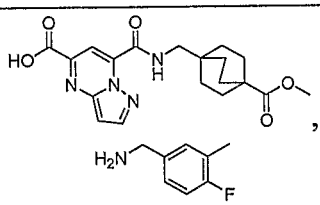
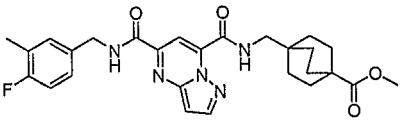
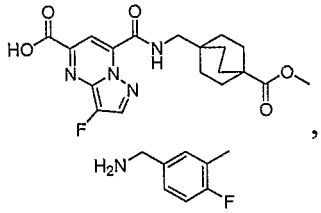
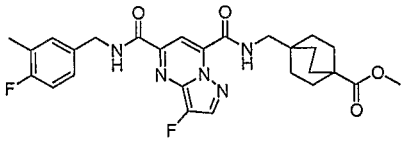
Ex. #	acid, amine	product	method, yield
127			C, 78% $[MH]^+ = 507$
128			C, 61% $[MH]^+ = 507$
129			C, 75% $[MH]^+ = 483$
130			C, 59% $[MH]^+ = 497$
131			C, 52% $[MH]^+ = 503$
132			C, 31% $[MH]^+ = 527$
133			C, 77% $[MH]^+ = 527$

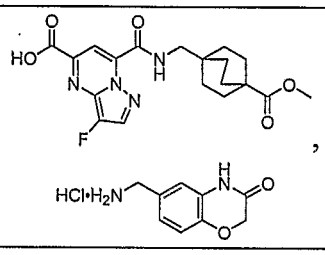
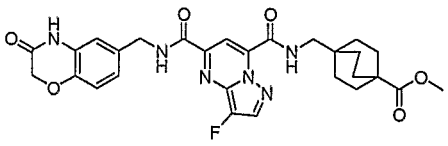
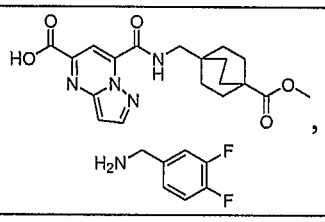
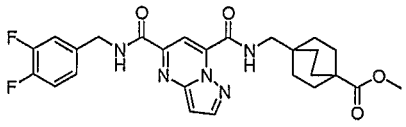
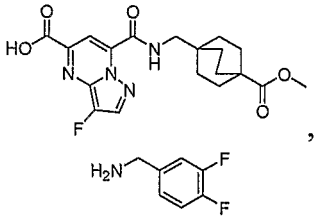
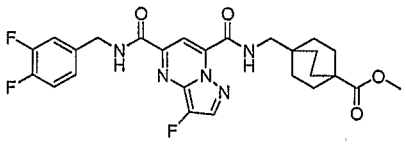
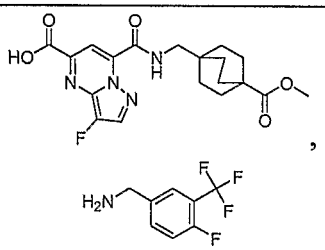
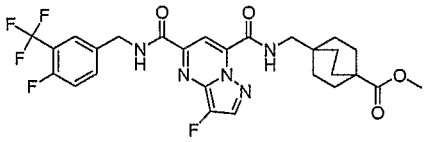
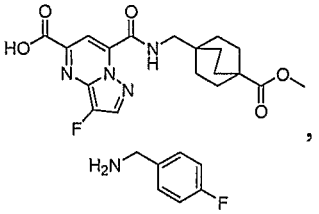
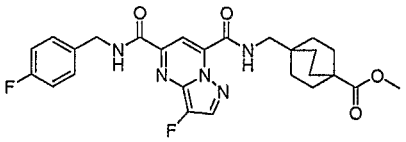
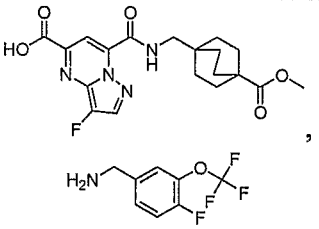
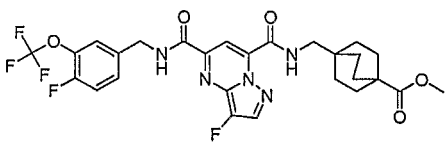
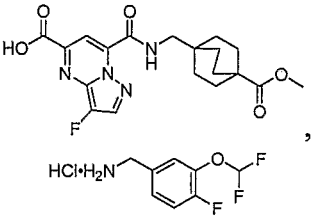
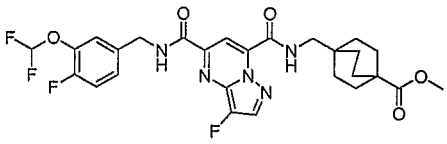
Ex. #	acid, amine	product	method, yield
134			C, 26% $[MH]^+ = 544$
135			C, 51% $[MH]^+ = 598$
136			C, 33% $[MH]^+ = 546$
137			C, 80% $[MH]^+ = 483$
138			C, 72% $[MH]^+ = 483$
139			C, 48% $[MH]^+ = 532$
140			C, 83% $[MH]^+ = 608$

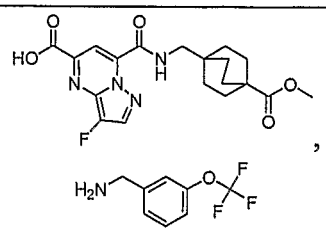
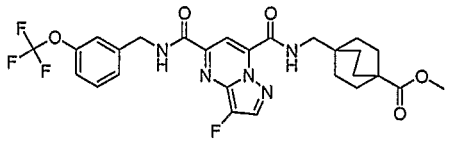
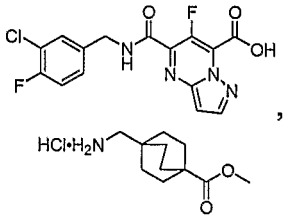
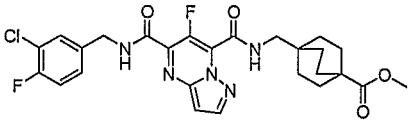
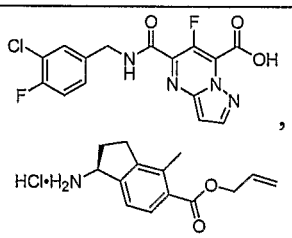
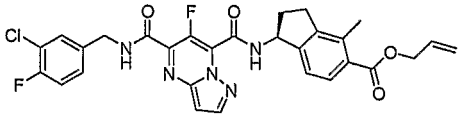
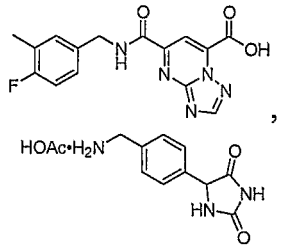
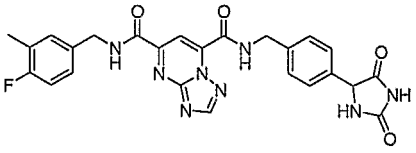
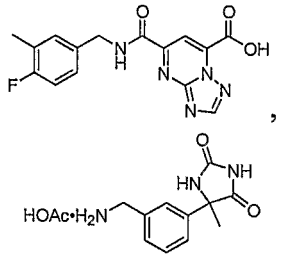
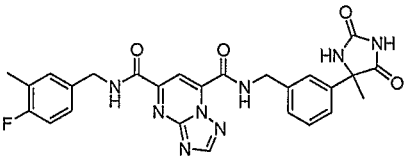
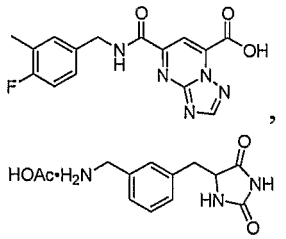
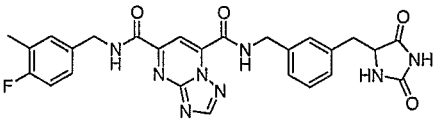
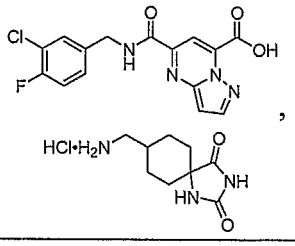
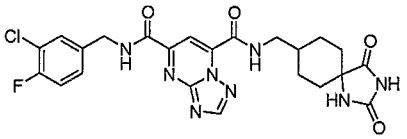
Ex. #	acid, amine	product	method, yield
141			C, 94% $[MH]^+ = 609$
142			C, 80% $[MH]^+ = 623$
143			C, 78% $[MH]^+ = 637$
144			C, 90% $[MH]^+ = 593$
145			C, 59% $[MH]^+ = 607$
146			C, 30% $[MH]^+ = 564$
147			C, 76% $[MH]^+ = 554$

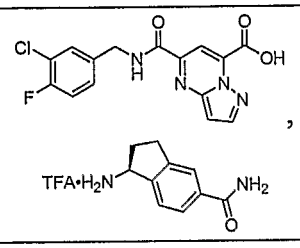
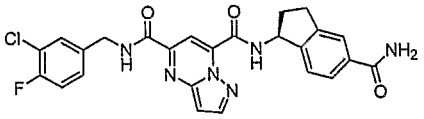
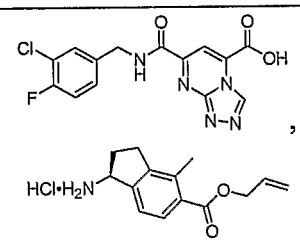
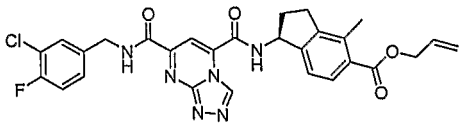
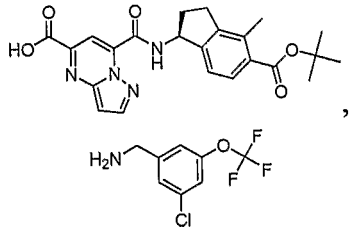
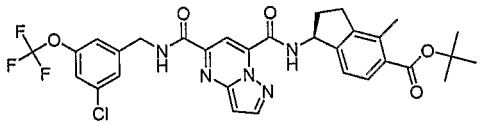
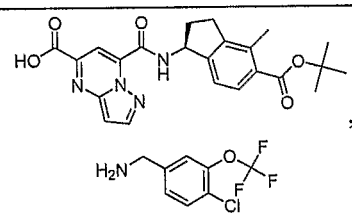
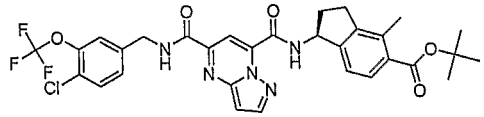
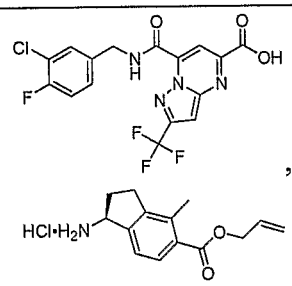
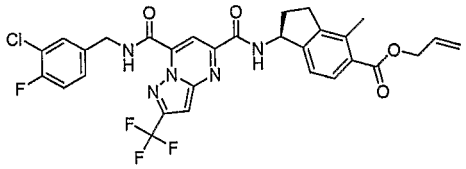
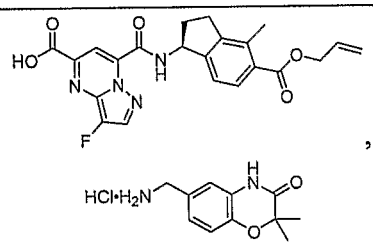
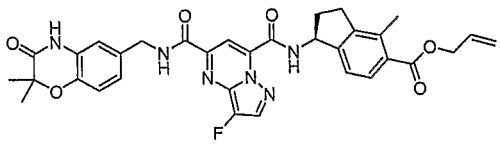
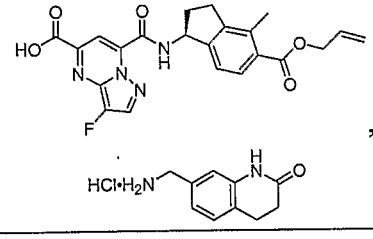
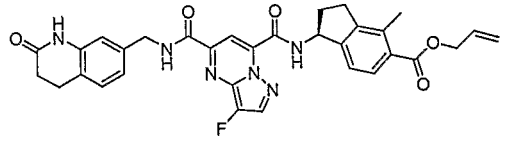
Ex. #	acid, amine	product	method, yield
148			C, 64% $[MH]^+ = 597$
149			C, 84% $[MH]^+ = 597$
150			C, 78% $[MH]^+ = 597$
151			C, 49% $[MH]^+ = 566$
152			C, 75% $[M-"indene"]^+ = 362$
153			C, 82% $[MH]^+ = 495$
154			C, 29% $[MH]^+ = 553$

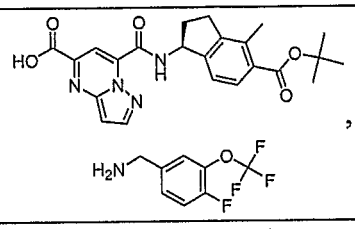
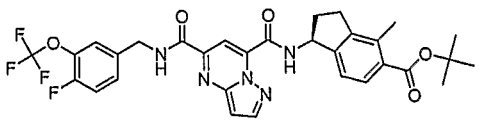
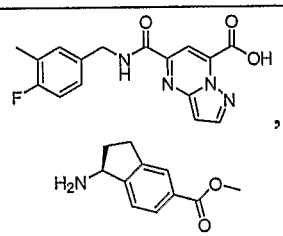
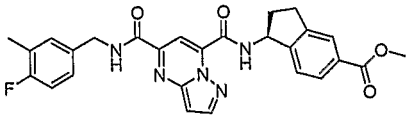
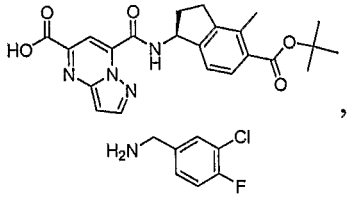
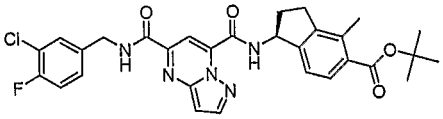
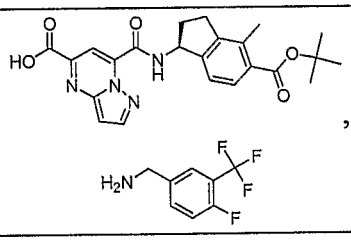
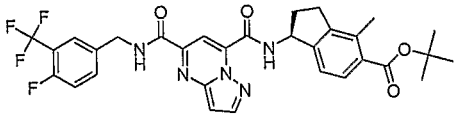
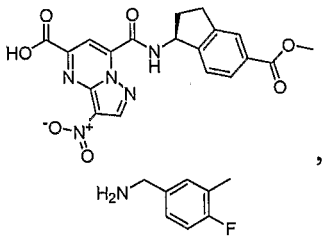
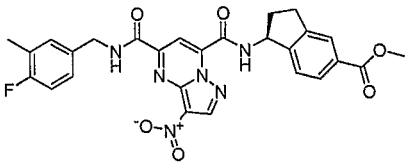
Ex. #	acid, amine	product	method, yield
155			C, 26% $[MH]^+ = 496$
156			C, 56% $[MH]^+ = 518$
157			C, 5% $[MH]^+ = 514$
158			C, 52% $[MH]^+ = 506$
159			C, 38% $[MH]^+ = 610$
160			C, 19% $[MH]^+ = 702$
161			C, 25% $[MH]^+ = 549/551$

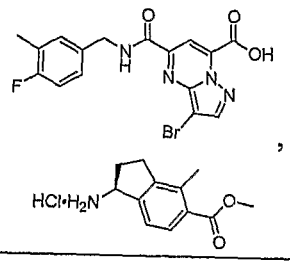
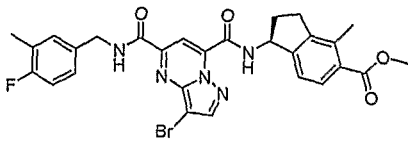
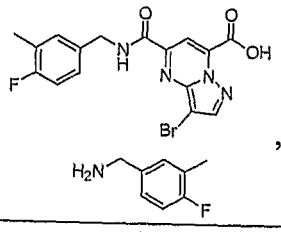
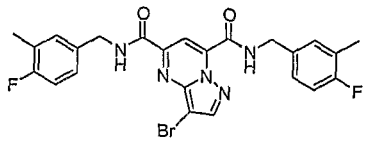
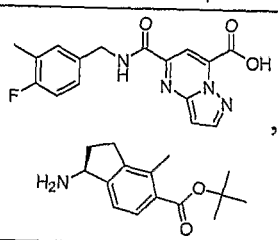
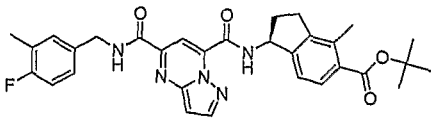
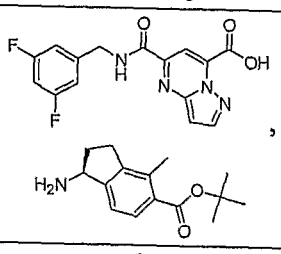
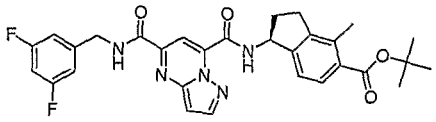
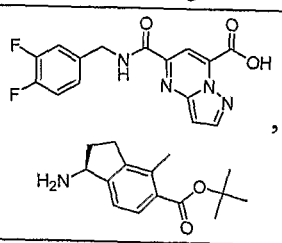
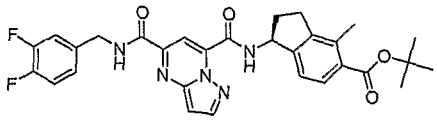
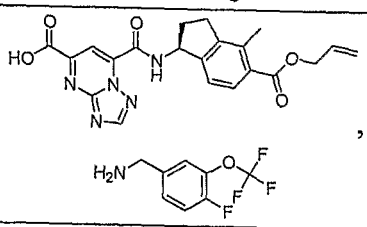
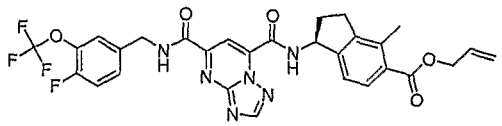
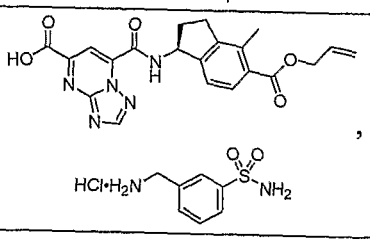
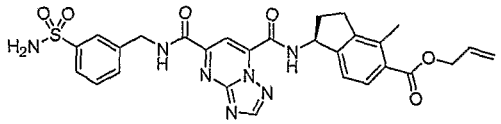
Ex. #	acid, amine	product	method, yield
162			C, 48% $[MH]^+ = 504$
163			C, 41% $[MH]^+ = 546$
164			C, 48% $[MH]^+ = 509$
165			C, 55% $[MH]^+ = 528$
166			C, 20% $[MH]^+ = 528$
167			C, 71% $[MH]^+ = 508$
168			C, 72% $[MH]^+ = 526$

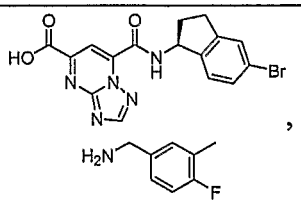
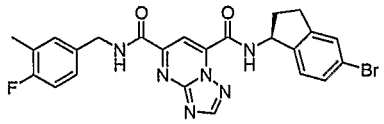
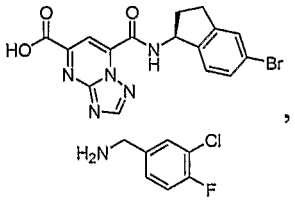
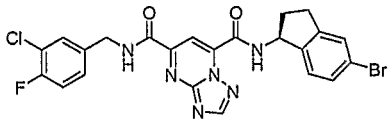
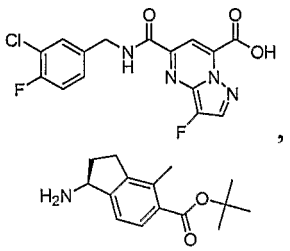
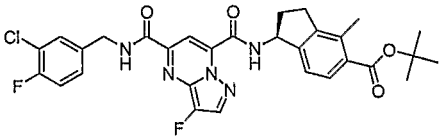
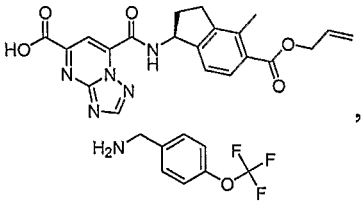
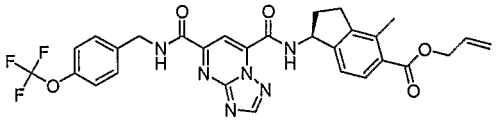
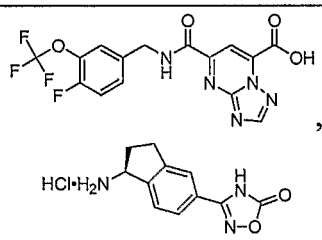
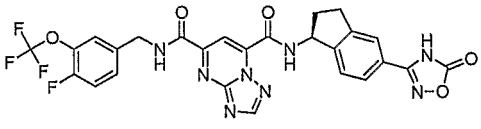
Ex. #	acid, amine	product	method, yield
169			C, 41% $[MH]^+ = 565$
170			C, 68% $[MH]^+ = 512$
171			C, 72% $[MH]^+ = 530$
172			C, 78% $[MH]^+ = 580$
173			C, 79% $[MH]^+ = 512$
174			C, 75% $[MH]^+ = 596$
175			C, 83% $[MH]^+ = 560$

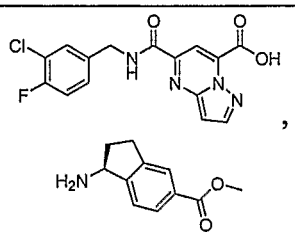
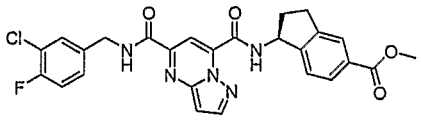
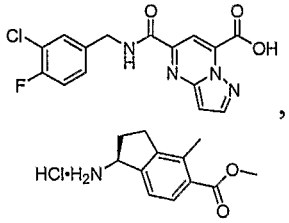
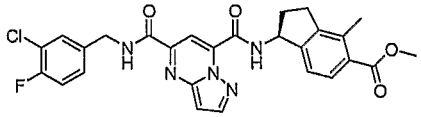
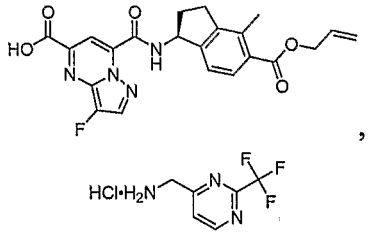
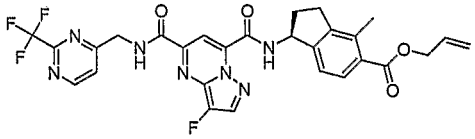
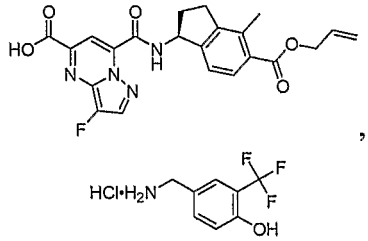
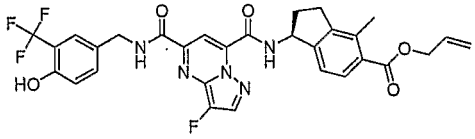
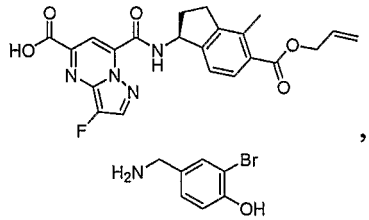
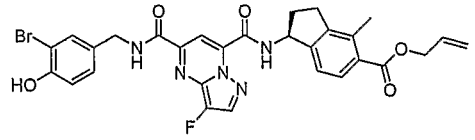
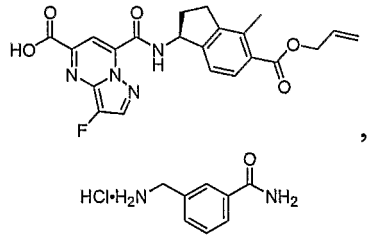
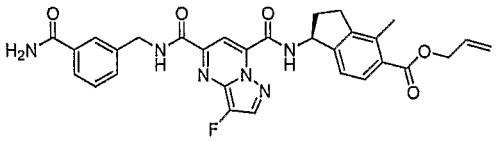
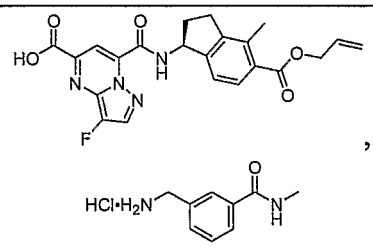
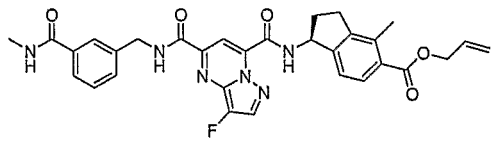
Ex. #	acid, amine	product	method, yield
176			C, 82% $[MH]^+ = 578$
177			C, 21% $[MH]^+ = 546$
178			C, 15% $[MH]^+ = 580$
179			E, 21% $[M-H]^- = 515$
180			E, 23% $[M-H]^- = 529$
181			E, 24% $[M-H]^- = 529$
182			E, 11% $[M-H]^- = 526$

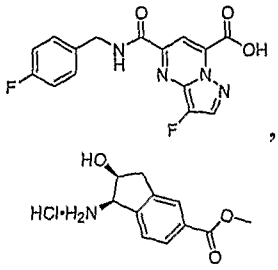
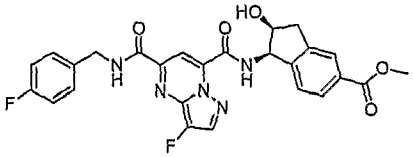
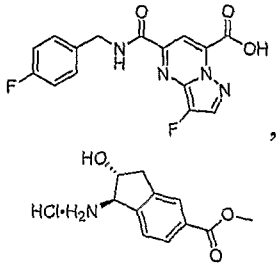
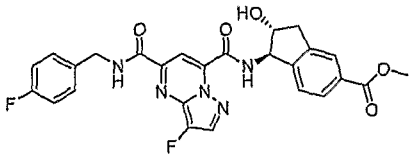
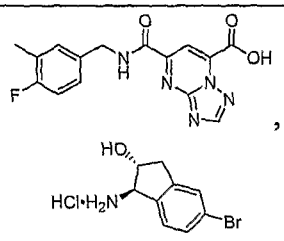
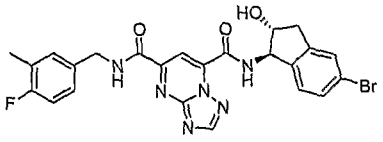
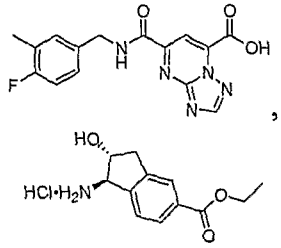
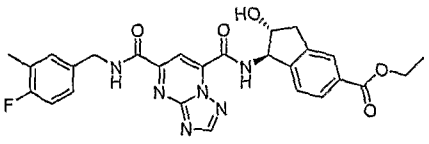
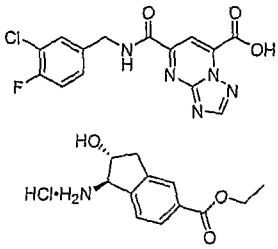
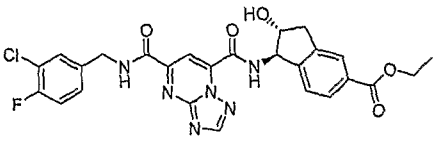
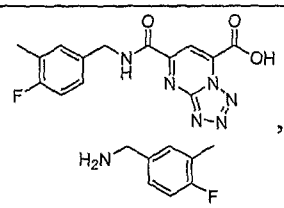
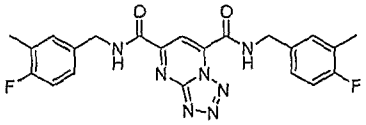
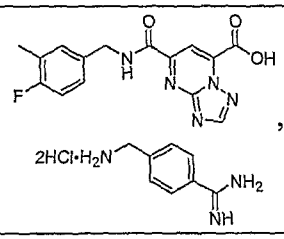
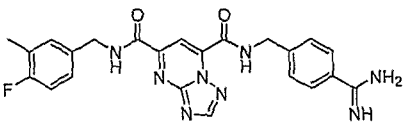
Ex. #	acid, amine	product	method, yield
183			E, 34% $[MH]^+ = 507$
184			E, 52% $[MH]^+ = 563$
185			E, n.d. $[MH]^+ = 644$
186			E, n.d. $[MH]^+ = 644$
187			E, 57% $[M-H]^- = 628$
188			B, n.d. $[MH]^+ = 627$
189			B, n.d. $[MH]^+ = 597$

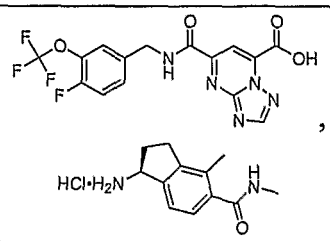
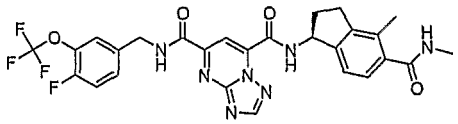
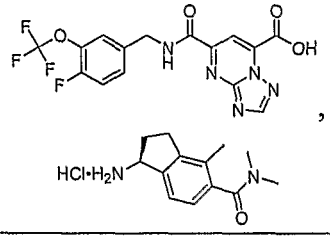
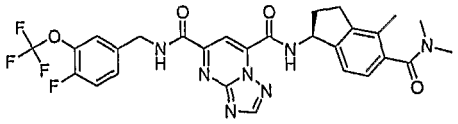
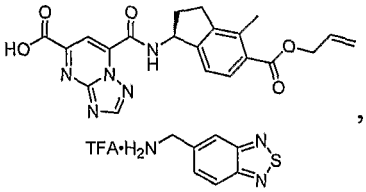
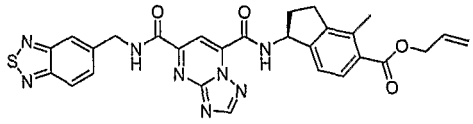
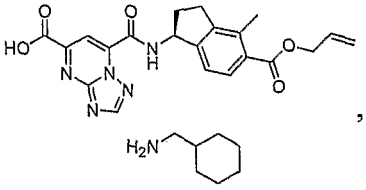
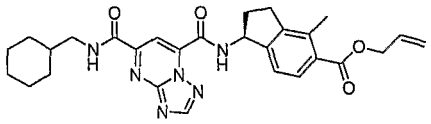
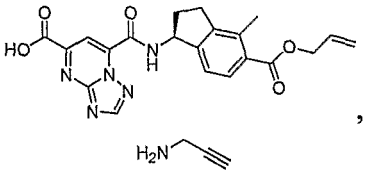
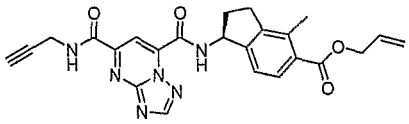
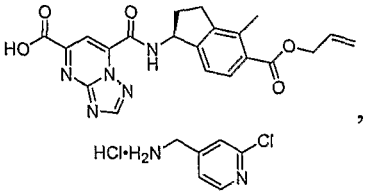
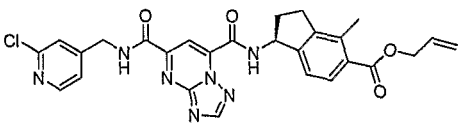
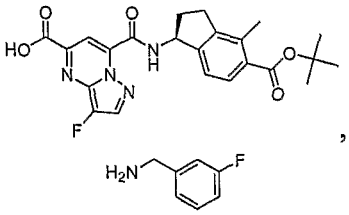
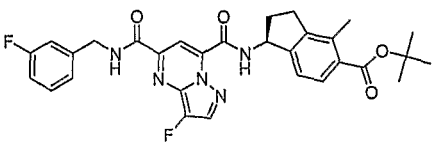
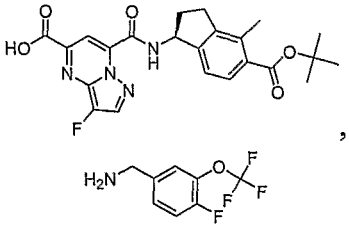
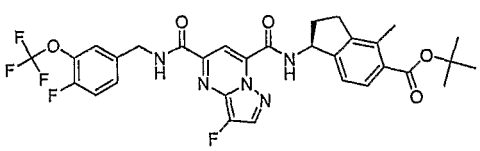
Ex. #	acid, amine	product	method, yield
190			D, 72% $[MH]^+ = 628$
191			A, 54% $[MH]^+ = 612$
192			A, 27% $[MH]^+ = 578$
193			A, 28% $[MH]^+ = 612$
194			A, 33% ^{1}H-NMR ($CDCl_3$) δ = 10.50 (br d, 1 H), 9.00 (s, 1 H), 8.85 (s, 1 H), 8.35 (br t, 1 H), 8.00 (s, 1 H), 7.95 (d, 1 H), 7.40 (d, 1 H), 7.25-7.00 (m, 2 H), 7.00-6.90 (m, 1 H), 5.80 (m, 1 H), 4.65 (br d, 2 H), 3.90 (s, 3 H), 3.20-2.70 (m, 3 H), 2.25 (s, 3 H), 2.20-2.00 (m, 1 H).

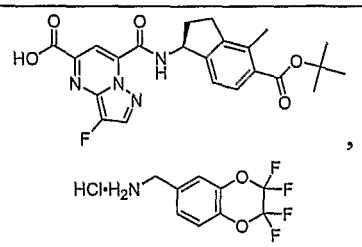
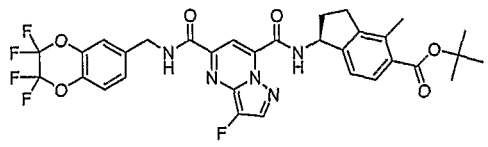
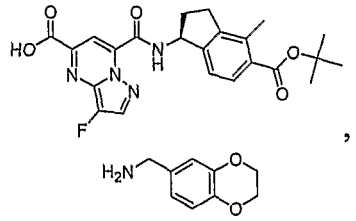
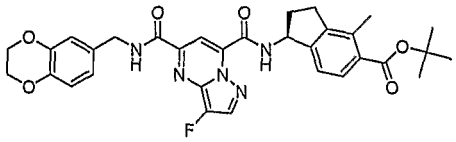
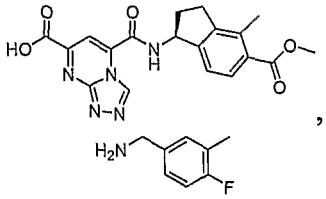
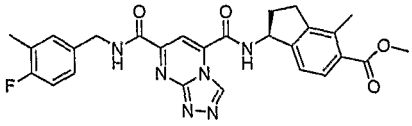
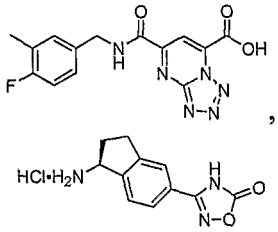
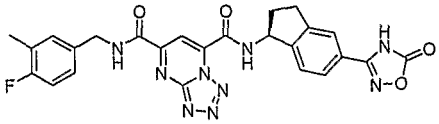
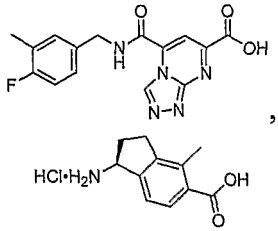
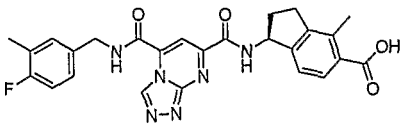
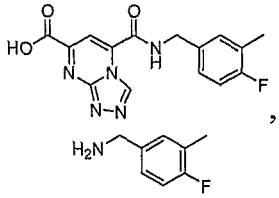
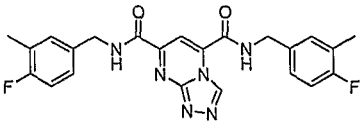
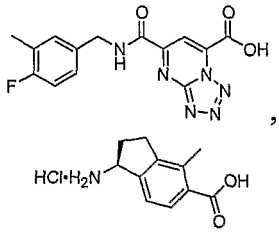
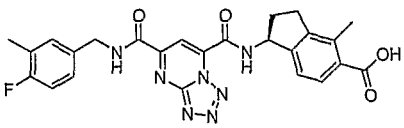
Ex. #	acid, amine	product	method, yield
195			A, n.d. $[MH]^+ = 594/596$
196			A, n.d. $MH]^+ = 528/530$
197			A, 43% $[MH]^+ = 558$
198			C, 66% $[MH]^+ = 562$
199			C, 44% $[MH]^+ = 562$
200			C, 48% $[MH]^+ = 613$
201			C, n.d. $[MH]^+ = 550$

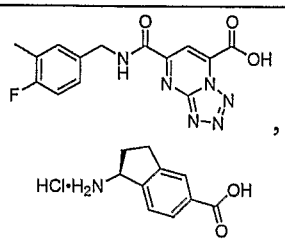
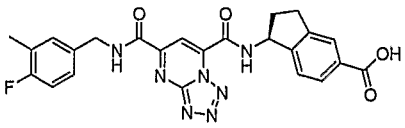
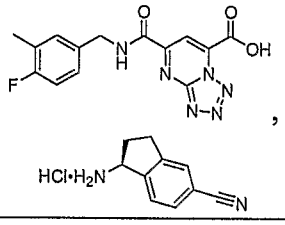
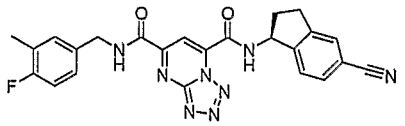
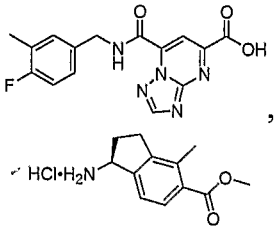
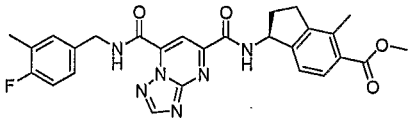
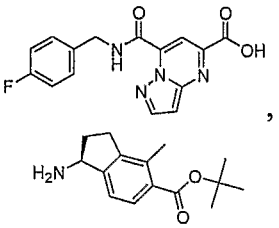
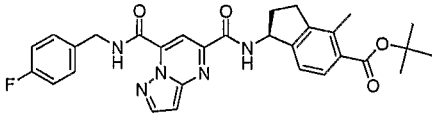
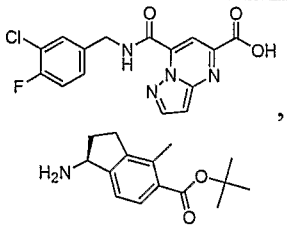
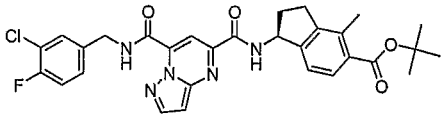
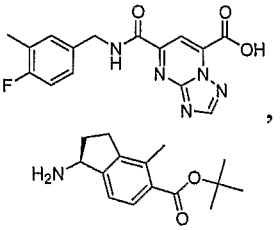
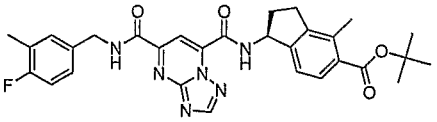
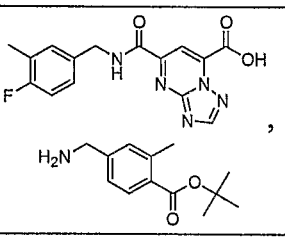
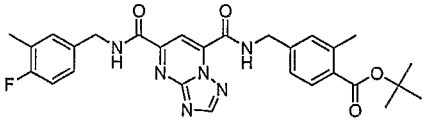
Ex. #	acid, amine	product	method, yield
202			C, 65% $[MH]^+ = 523/525$
203			C, 52% $[MH]^+ = 543/545$
204			C, 54% ^{1}H-NMR ($CDCl_3$) δ = 10.25 (br d, 1 H), 8.60 (s, 1 H), 8.10 (m, 1 H), 8.00 (d, 1 H), 7.60 (d, 1 H), 7.30 (d, 1 H), 7.20-7.10 (m, 2 H), 7.10-7.00 (m, 1 H), 5.70 (m, 1 H), 4.55 (d, 2 H), 3.10-2.60 (m, 3 H), 2.40 (s, 9 H), 2.00-1.90 (m, 1 H).
205			C, 70% $[MH]^+ = 595$
206			C, 79% $[MH]^+ = 599$

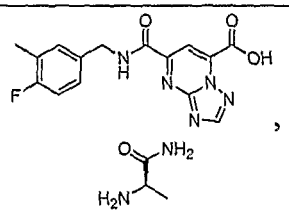
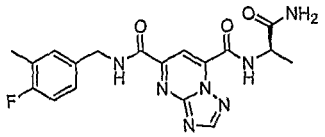
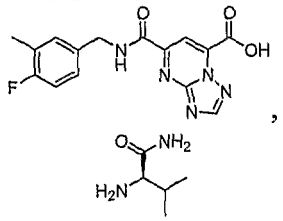
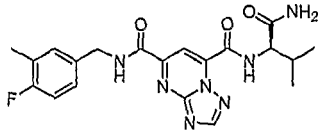
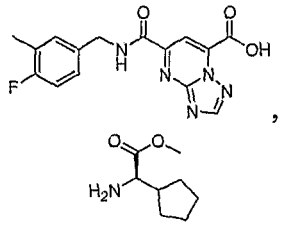
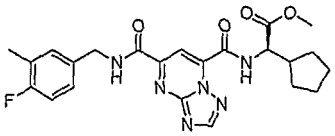
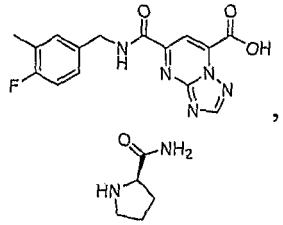
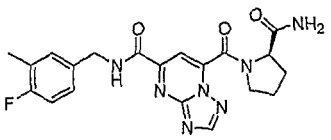
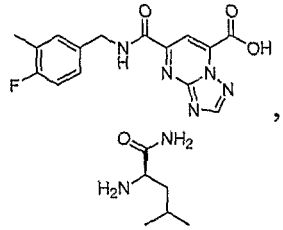
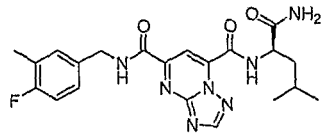
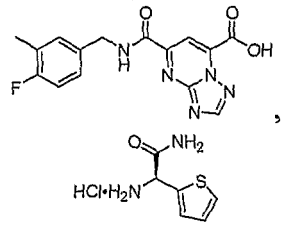
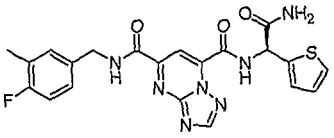
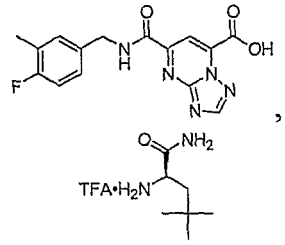
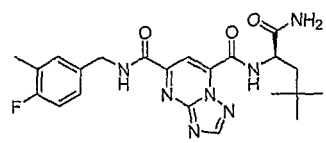
Ex. #	acid, amine	product	method, yield
207			C, 55% $[MH]^+ = 522$
208			C, 59% $[MH]^+ = 536$
209			C, 63% $[MH]^+ = 598$
210			C, 32% $[M-"indene"]^+ = 398$
211			C, 66% $[MH]^+ = 623$
212			C, 61% $[MH]^+ = 571$
213			C, 86% $[MH]^+ = 585$

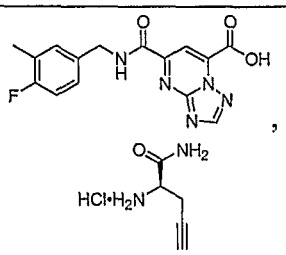
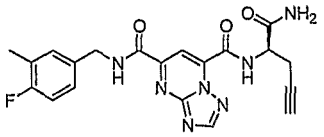
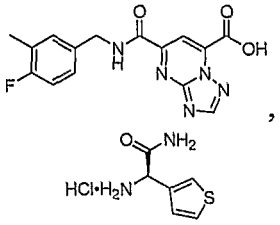
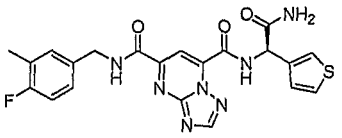
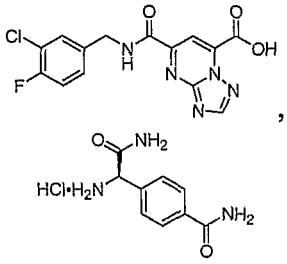
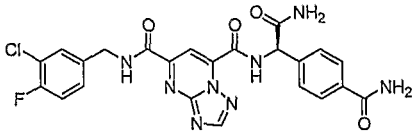
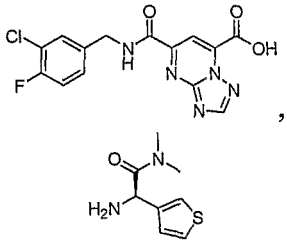
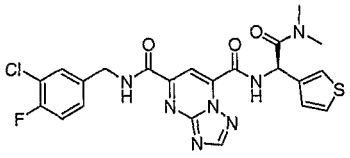
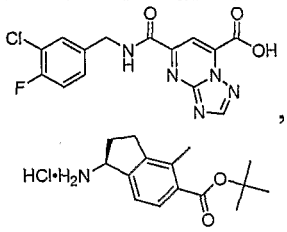
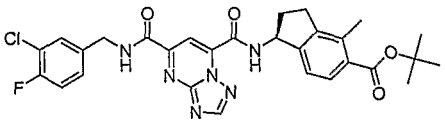
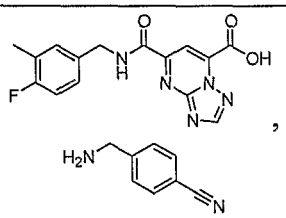
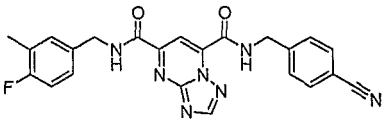
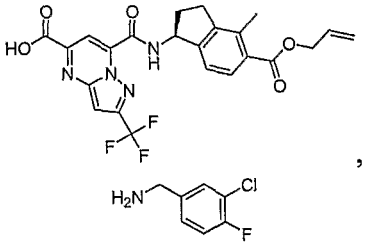
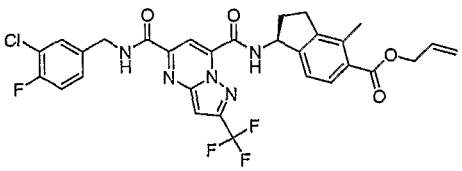
Ex. #	acid, amine	product	method, yield
214			E, 60% $[M-H]^-$ = 520
215			E, 65% $[M-H]^-$ = 520
216			E, 49% $[MH]^+$ = 539/541
217			E, 90% $[MH]^+$ = 533
218			E, 80% $[MH]^+$ = 550
219			C, 45% $[MH]^+$ = 452
220			C, 43% $[MH]^+$ = 461

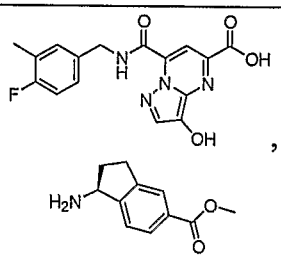
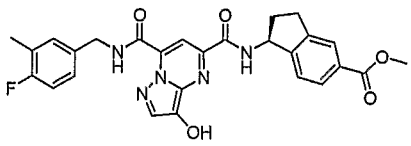
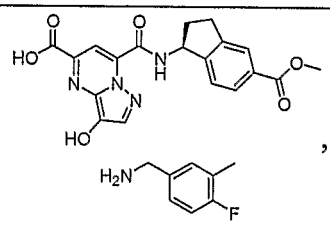
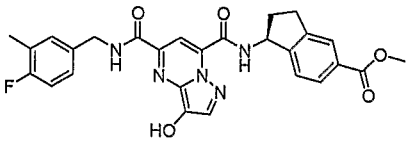
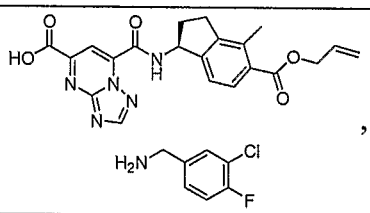
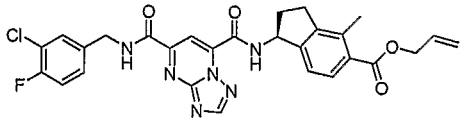
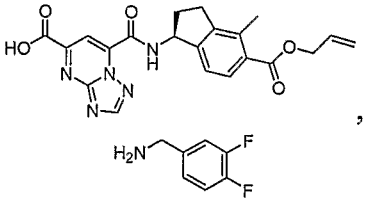
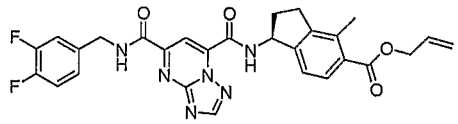
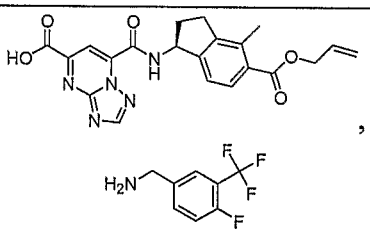
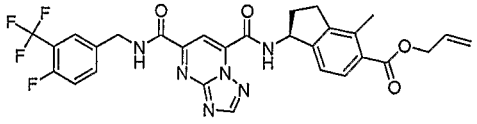
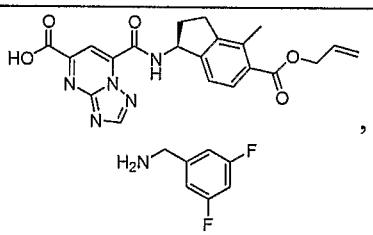
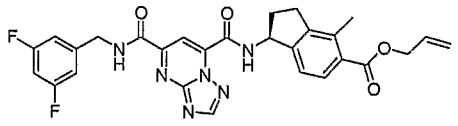
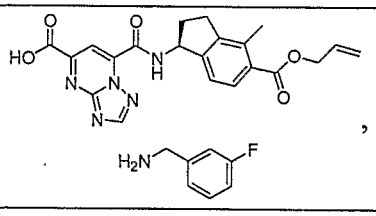
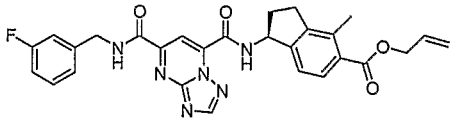
Ex. #	acid, amine	product	method, yield
221			C, 46% $[MH]^+ = 572$
222			C, 47% $[MH]^+ = 586$
223			C, n.d. $[MH]^+ = 569$
224			C, n.d. $[MH]^+ = 517$
225			C, n.d. $[MH]^+ = 459$
226			C, n.d. $[MH]^+ = 546$
227			C, n.d. $[MNa]^+ = 584$
228			C, n.d. $[MNa]^+ = 669$

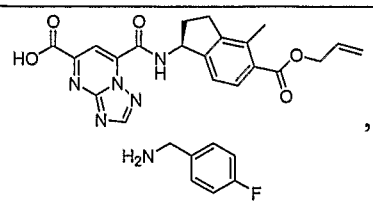
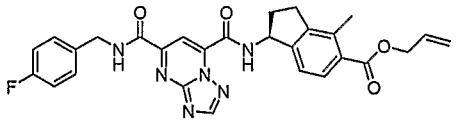
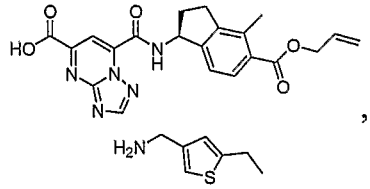
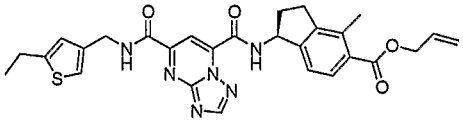
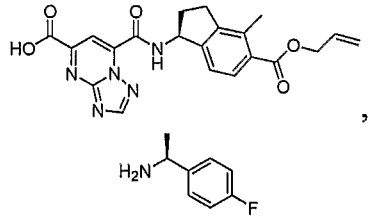
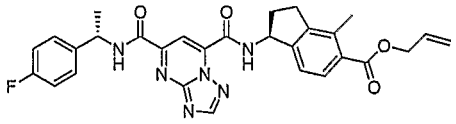
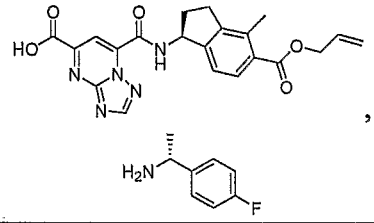
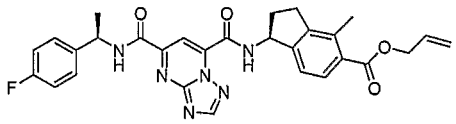
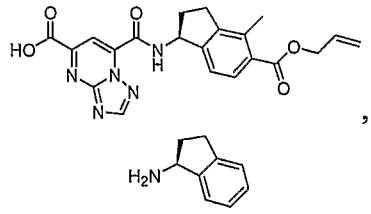
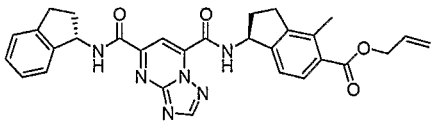
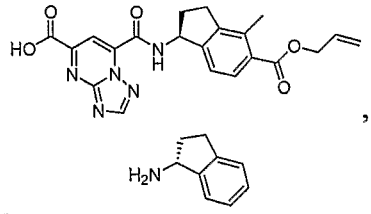
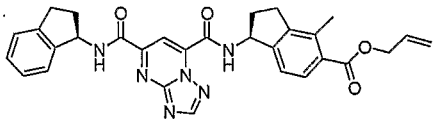
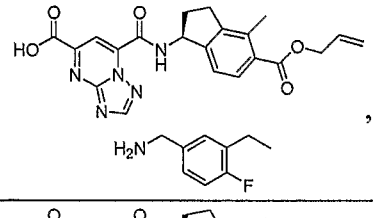
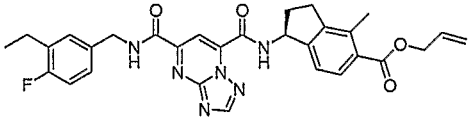
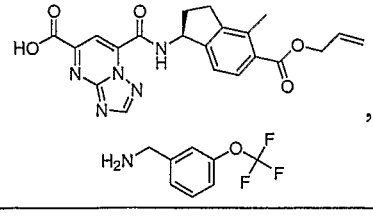
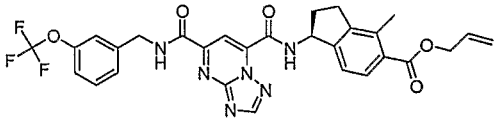
Ex. #	acid, amine	product	method, yield
229			C, n.d. $[MNa]^+ = 696$
230			C, n.d. $[MNa]^+ = 624$
231			C, 60% (over 2 steps), $[MH]^+ = 517$
232			A, 51% $[MH]^+ = 530$
233			A, 7% (over 2 steps), $[MH]^+ = 451$
234			A, 20% (over 2 steps), $[MH]^+ = 451$
235			E, 35% $[M-H]^- = 502$

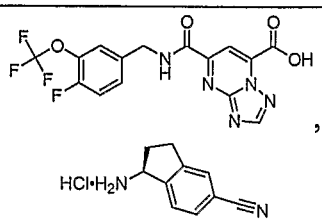
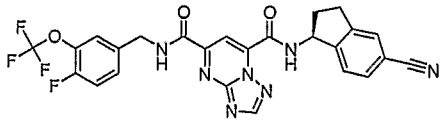
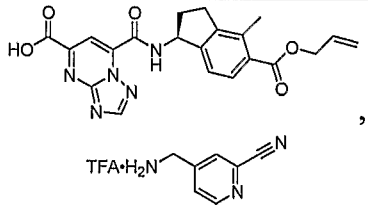
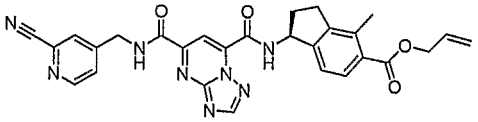
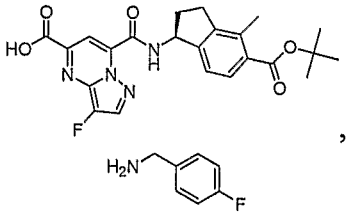
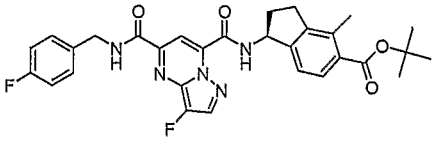
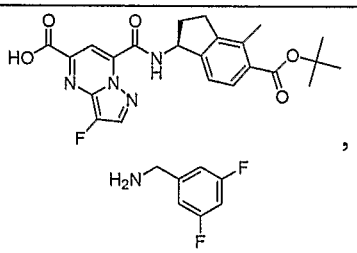
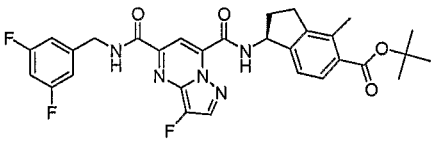
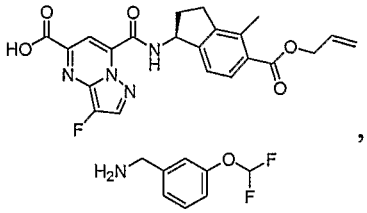
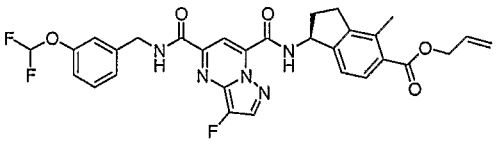
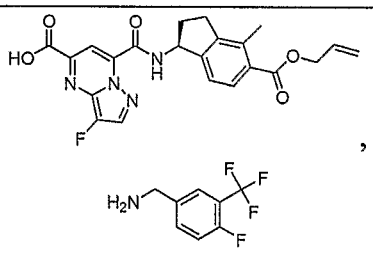
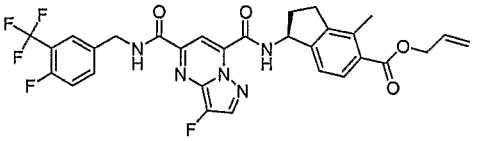
Ex. #	acid, amine	product	method, yield
236			E, 29% $[M-H]^- = 488$
237			A, 98% $[MH]^+ = 471$
238			A, 16% $[MH]^+ = 517$
239			E, 52% $[MNa]^+ = 566$
240			E, 31% $[M-H]^- = 576$
241			A, n.d. $[MH]^+ = 599$
242			E, 51% $[MH]^+ = 533$

Ex. #	acid, amine	product	method, yield
243			E, 50% $[MH]^+ = 462$
244			E, 40% $[MH]^+ = 428$
245			E, 30% $[MH]^+ = 469$
246			E, 10% $[MH]^+ = 426$
247			E, 34% $[MH]^+ = 442$
248			E, 20% $[MH]^+ = 468$
249			E, 30% $[MH]^+ = 456$

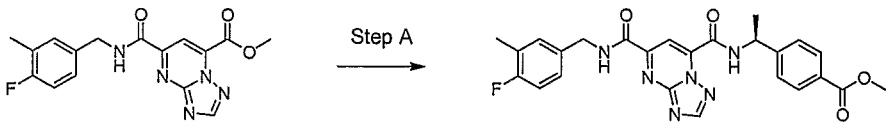
Ex. #	acid, amine	product	method, yield
250			E, 25% $[MH]^+ = 424$
251			E, 30% $[MH]^+ = 468$
252			E, 34% $[MH]^+ = 525$
253			E, 18% $[MH]^+ = 516$
254			E, n.d. $[MH]^+ = 579$
255			E, 42% $[MH]^+ = 444$
256			E, 70% $[MH]^+ = 630$

Ex. #	acid, amine	product	method, yield
257			C, 10% $[MH]^+ = 518$
258			C, 29% $[MH]^+ = 518$
259			C, 96% $[MH]^+ = 564$
260			C, 91% $[MH]^+ = 547$
261			C, n.d. $[MH]^+ = 597$
262			C, 93% $[MH]^+ = 547$
263			C, 81% $[MH]^+ = 529$

Ex. #	acid, amine	product	method, yield
264			C, 86% $[MH]^+ = 529$
265			C, 76% $[MH]^+ = 545$
266			C, n.d. $[MH]^+ = 543$
267			C, n.d. $[MH]^+ = 543$
268			C, n.d. $[MH]^+ = 537$
269			C, n.d. $[MH]^+ = 537$
270			C, n.d. $[MH]^+ = 557$
271			C, n.d. $[MH]^+ = 595$

Ex. #	acid, amine	product	method, yield
272			C, 38% $[MH]^+ = 540$
273			C, n.d. $[MH]^+ = 537$
274			C, n.d. $[MNa]^+ = 584$
275			C, n.d. $[MNa]^+ = 602$
276			C, n.d. $[MH]^+ = 594$
277			C, n.d. $[MH]^+ = 614$

Example 278



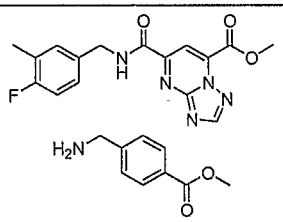
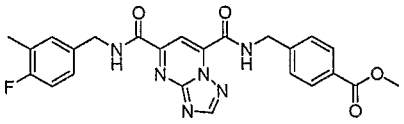
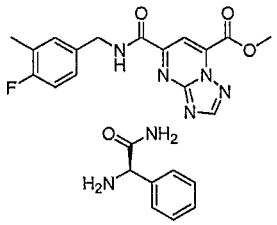
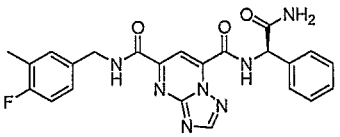
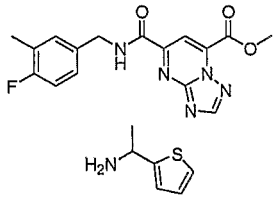
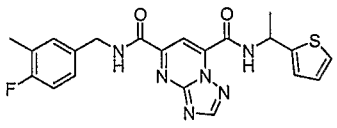
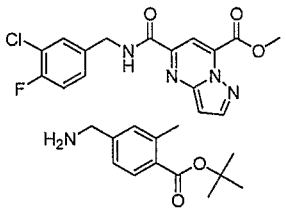
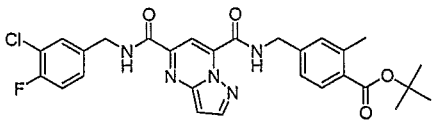
[0542] Step A

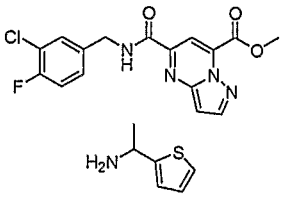
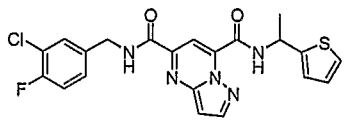
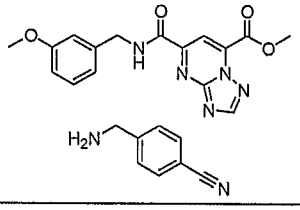
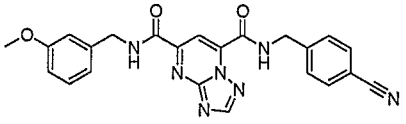
To a solution of the title compound from the Preparative Example 315 (67 mg) in anhydrous DMF (500 μL) was added a solution of the title compound from the Preparative Example 229, Step D (75 mg). The resulting mixture was heated at 60°C for 15 h, concentrated and purified by preparative thin layer chromatography (silica, CH_2Cl_2/MeOH) to give the desired title compound (39 mg, 41%). $[MH]^+ = 491$.

Examples 279-284

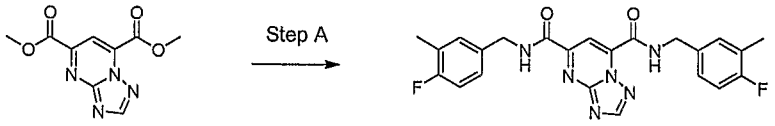
[0543] Following a similar procedure as described in the Example 278, except using the esters and amines indicated in Table II-2 below, the following compounds were prepared.

Table II-2

Ex. #	ester, amine	product	yield
279			47% $[MH]^+ = 477$
280			48% $[MH]^+ = 462$
281			43% $[MH]^+ = 439$
282			60% $[MH]^+ = 552$

Ex. #	ester, amine	product	yield
283			50% $[MH]^+ = 458$
284			53% $[MH]^+ = 442$

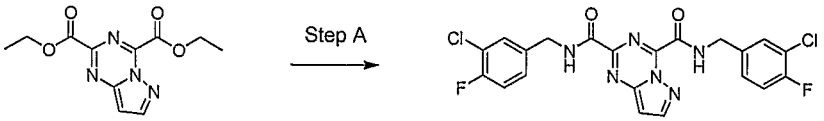
Example 285



[0544] Step A

To a solution of the title compound from the Preparative Example 244, Step A (200 mg) in anhydrous DMF (2 mL) was added commercially available 4-fluoro-3-methyl-benzylamine (120 mg). The resulting mixture was heated at 60°C for 24 h, concentrated and purified by preparative thin layer chromatography (silica, CH_2Cl_2/MeOH) to give the title compound (30 mg, 8%). $[MH]^+ = 452$.

Example 286

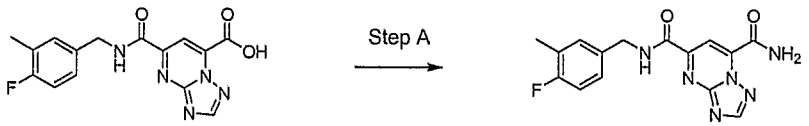


[0545] Step A

A mixture of the title compound Preparative Example 330, Step A (203 mg) and commercially available 3-chloro-4-fluorobenzylamine (160 mg) in dry DMF (3 mL) was heated to 70°C overnight and concentrated. The remaining residue was dissolved in $CHCl_3$, washed with 10% aqueous citric acid and saturated aqueous NaCl, dried ($MgSO_4$), filtered,

concentrated and purified by preparative thin layer chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a colorless solid (111 mg, 29%). $[MH]^+ = 492$.

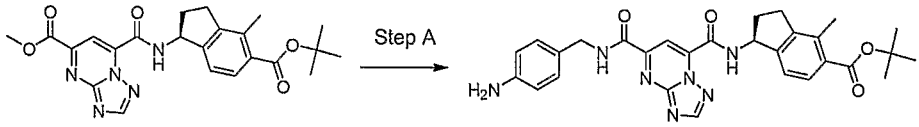
Example 287



[0546] Step A

A solution of the title compound from the Preparative Example 331, Step A (26 mg) in a 7M solution of NH_3 in MeOH (1 mL) was heated at 90°C for 2 h. The formed precipitate was isolated by filtration to afford the title compound as a colorless solid (8.6 mg, 34%). $[MH]^+ = 329$.

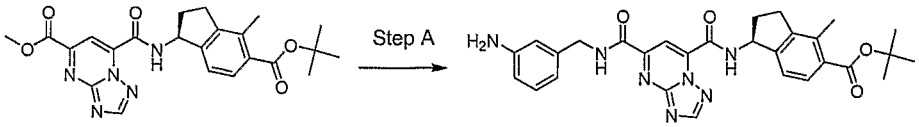
Example 288



[0547] Step A

The title compound from the Preparative Example 294 (9.7 mg) and commercially available 4-aminomethyl-phenylamine (10 mg) were dissolved in *N*-methylpyrrolidin-2-one (0.5 mL). The mixture was heated in a sealed tube at 160°C (microwave) for 15 min, diluted with EtOAc, washed with aqueous LiCl, concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (9.6 mg, 84%). $[M-H]^- = 540$.

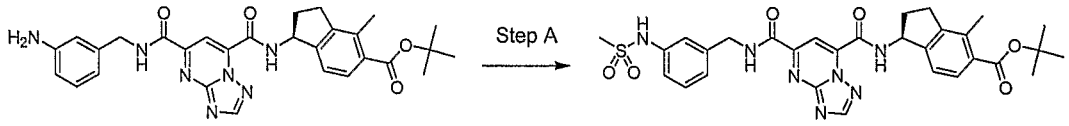
Example 289



[0548] Step A

The title compound from the Preparative Example 294 (154 mg) and commercially available 3-aminomethyl-phenylamine (57 mg) were dissolved in *N*-methylpyrrolidin-2-one (3 mL). The mixture was heated in a sealed tube at 160°C (microwave) for 55 min, diluted with EtOAc, washed with aqueous LiCl, concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (110 mg, 84%). $[M-H]^- = 540$.

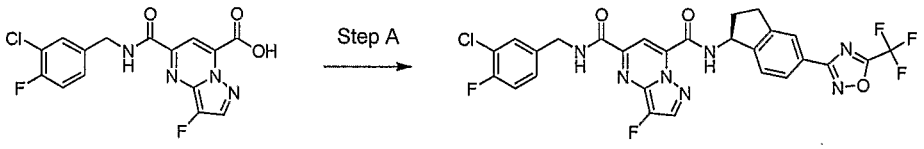
Example 290



[0549] Step A

To a solution of the title compound from the Example 289, Step A (19.1 mg) in CH_2Cl_2 (1 mL) were successively added pyridine (0.1 mL) and methanesulfonyl chloride (8.1 mg). The mixture was stirred for 1 d, concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (13.1 mg, 60%). $[M-H]^- = 618$.

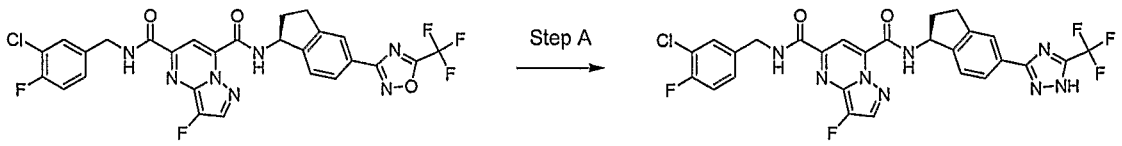
Example 291



[0550] Step A

To a solution of the title compound from the Preparative Example 342 (51 mg) in THF (5 mL) were added the title compound from the Preparative Example 149, EDCI (53 mg), HOBt (38 mg) and K_2CO_3 (44 mg). The mixture was stirred for 16 h, absorbed on silica (500 mg) and purified by chromatography (silica, hexanes/EtOAc) to afford the title compound as a solid (79.3 mg, 92%). $[M-H]^- = 616$.

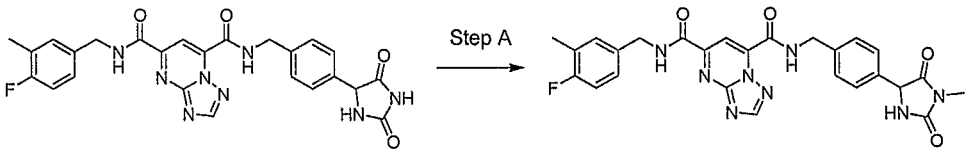
Example 292



[0551] Step A

To a solution of the title compound from the Example 291, Step A (50 mg) in $MeOH/CH_2Cl_2$ (1:1, 2 mL) was added hydrazine (26 mg). The resulting mixture was stirred for 1 d, concentrated and and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a yellow solid. (37.1 mg, 74%). $[M-H]^- = 615$.

Example 293



[0552] Step A

To a solution of the title compound from the Example 179 (2.5 mg) in toluene/MeOH (3:1, 2 mL) was added a 2M solution of (trimethylsilyl)diazomethane in Et_2O (portions à 10 μL) until complete consumption of the starting material. The mixture was concentrated and then triturated with Et_2O (4 x) to give the title compound as a yellow solid (1.0 mg, 40%). $[M-H]^- = 529$.

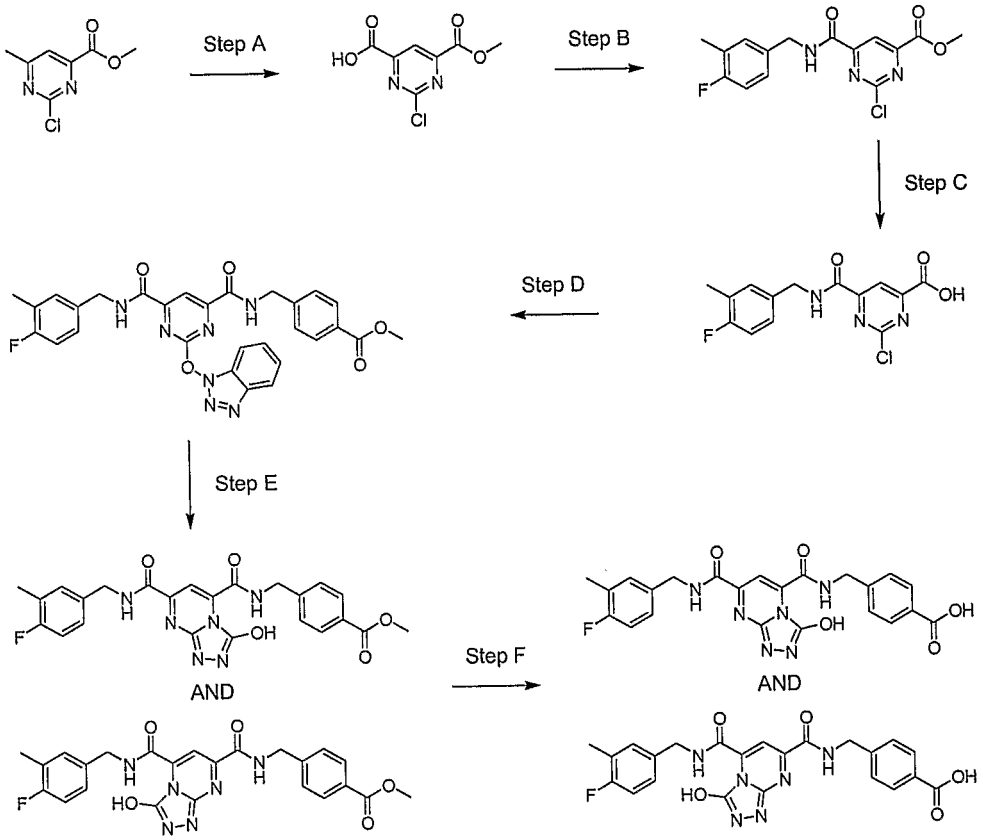
Example 294



[0553] Step A

A mixture of the title compound from the Example 196 (52 mg) and Pd/C (10wt%, 20 mg) in MeOH/EtOAc (1:1, 4 mL) was hydrogenated at atmospheric pressure for 18 h, filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/acetone) to afford the title compound (19 mg, 43%). $[MH]^+ = 450$.

Example 295



[0554] Step A

Under an argon atmosphere a mixture of commercially available 2-chloro-6-methyl-pyrimidine-4-carboxylic acid methyl ester (9.38 g) and selenium dioxide (8.93 g) in 1,4-dioxane (50 mL) was stirred at 105°C for 12 h. The mixture was filtered twice through celite®, the filter cake was rinsed with 1,4-dioxane (2 x 100 mL) and the combined filtrates were concentrated to afford the title compound as viscous orange oil (8.0 g, 74%). $[MH]^+ = 217$.

[0555] Step B

To an ice cooled solution of the title compound from Step A above (900 mg) in anhydrous CH_2Cl_2 (20 mL) were subsequently and slowly added oxalyl chloride (870 μL) and DMF (3 drops). The cooling bath was removed and the mixture was stirred at room temperature until gas evolution ceased. The mixture was then concentrated and diluted with CH_2Cl_2. Pyridine (340 μL) and commercially available 4-fluoro-3-methylbenzylamine (530 μL) were added subsequently and the mixture was stirred at room temperature for 30 min. Filtration, absorption onto silica and purification by chromatography (silica, hexane/EtOAc) afforded the title compound as a yellow solid (670 mg, 48%). $[MH]^+ = 338$.

[0556] Step C

To an ice cooled solution of the title compound from Step B above (670 mg) in THF (20 mL) was slowly added 1M aqueous LiOH (3.98 mL). The mixture was stirred at 0°C for 2 h, quenched with 1M aqueous HCl (4.0 mL), warmed to room temperature and concentrated. The remaining residue was triturated with THF, filtered and concentrated to afford the title compound as an orange solid. $[MH]^+ = 324$.

[0557] Step D

The title compound from Step C above (256 mg), commercially available 4-aminomethyl-benzoic acid methyl ester hydrochloride (160 mg), PyBOP (800 mg) and NEt_3 (202 μL) were dissolved in THF/DMF (2:1, 15 mL). The mixture was stirred at room temperature for 2 h, concentrated, diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/acetone) to afford the title compound (196 mg, 44%). $[MH]^+ = 570$.

[0558] Step E

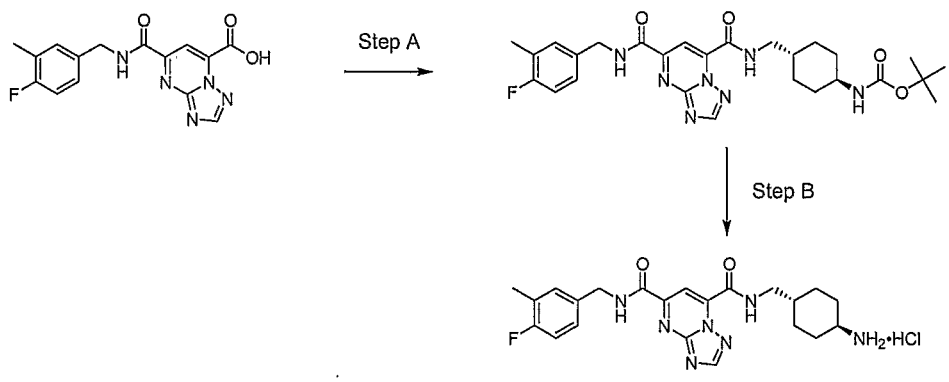
To a stirred solution of the title compound from Step D above (50 mg) in anhydrous THF (5 mL) was added hydrazine hydrate (40 μL). The mixture was stirred at room temperature for 2 h and then concentrated. The residue was dissolved in anhydrous 1,2-dichloroethane (2 mL) and cooled to 0°C. A 20% solution of phosgene in toluene (500 μL) was added, the cooling bath was removed and the mixture was stirred at room

temperature for 2 h. Concentration afforded the crude title compound as a mixture of two isomers, which was used without further purification. $[MH]^+ = 493$.

[0559] Step F

To a solution of the title compound from Step E above (30 mg) in THF/MeOH (2:1, 1.5 mL) was added 1N aqueous LiOH (0.2 mL). The mixture was stirred at room temperature overnight, adjusted to pH 4.5 with 2N aqueous HCl and extracted with EtOAc. The organic phase was washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by preparative thin layer chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a mixture of two isomers (3 mg, 8% over 2 steps). $[MH]^+ = 479$.

Example 296



[0560] Step A

To a solution of the title compound from the Preparative Example 331, Step A (329 mg) in DMF (10 mL) were successively added HATU (427 mg), HOAt (153 mg), commercially available *trans*-(4-aminomethyl-cyclohexyl)-carbamic acid *tert*-butyl ester (291 mg) and $^iPr_2NEt$ (191 μL) and the mixture was stirred at room temperature for 5 h. Additional HATU (427 mg), *trans*-(4-aminomethyl-cyclohexyl)-carbamic acid *tert*-butyl ester (291 mg) and $^iPr_2NEt$ (191 μL) were successively added and stirring at room temperature was continued for 2 h. The mixture was diluted with EtOAc (100 mL), washed with 0.01N aqueous HCl (3 x 100 mL) and saturated aqueous NaCl (100 mL), dried ($MgSO_4$) and filtered. The filter cake was rinsed with CH_2Cl_2/MeOH (95:5, 500 mL) and the combined filtrates were concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a colorless solid (493 mg, 91%). $[MNa]^+ = 562$.

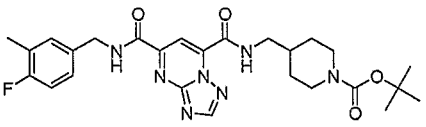
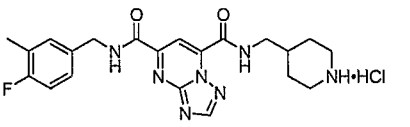
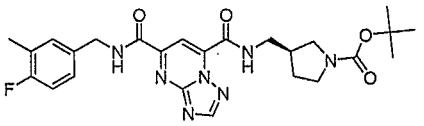
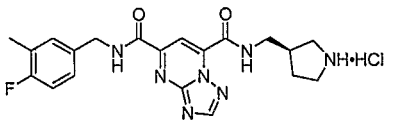
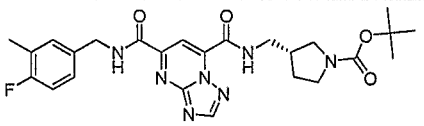
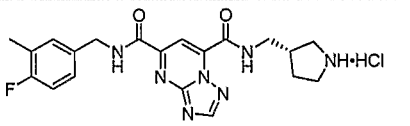
[0561] Step B

To a suspension of the title compound from Step A above (436 mg) in EtOAc (3.22 mL) was added a 4M solution of HCl in 1,4-dioxane (3.22 mL). The reaction mixture was stirred at room temperature for 2½ h, diluted with MeOH (10 mL), concentrated, suspended in CH_3CN/MeOH (4:1, 20 mL) and concentrated again to afford the title compound (384 mg, 99%). $[M\text{-}Cl]^+ = 440$.

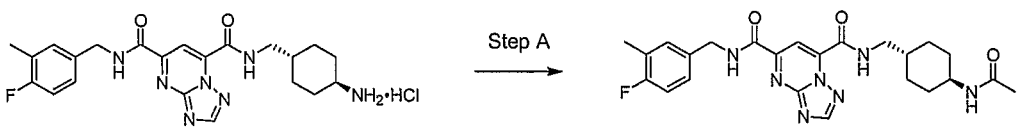
Examples 297-298(a)

[0562] Following a similar procedure as described in the Example 296, Step B, except using the protected amines indicated in Table II-3 below, the following compounds were prepared.

Table II-3

Ex. #	protected amine	product	yield
297			>99% $[M\text{-}Cl]^+ = 426$
298			98% $[M\text{-}Cl]^+ = 412$
298(a)			98% $[M\text{-}Cl]^+ = 412$

Example 299



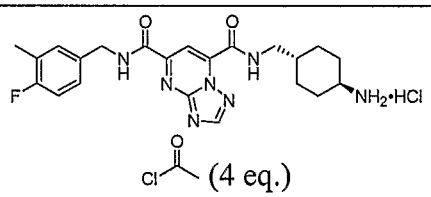
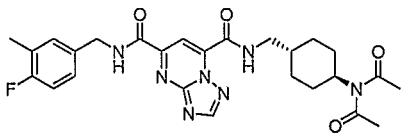
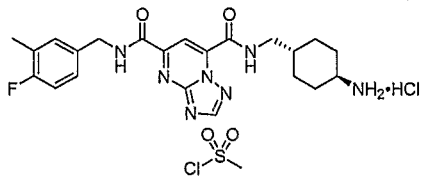
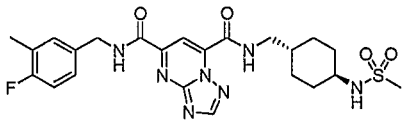
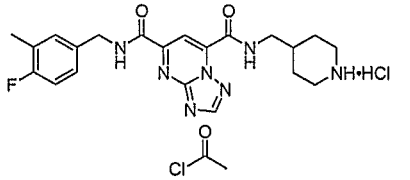
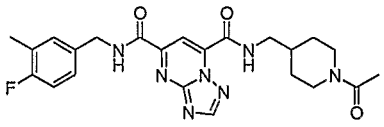
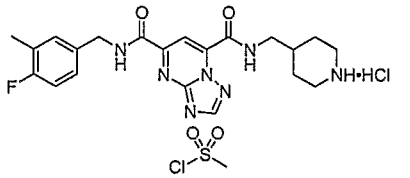
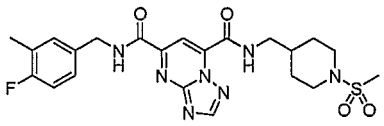
[0563] Step A

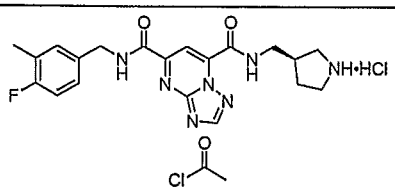
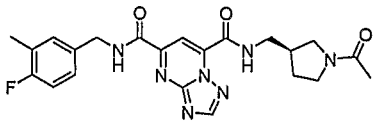
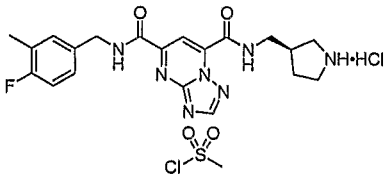
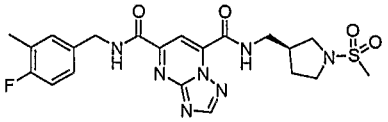
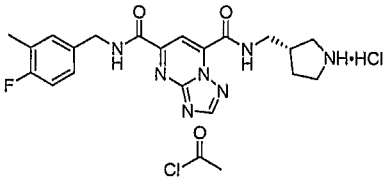
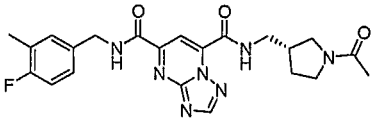
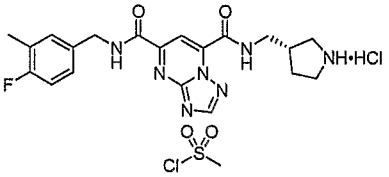
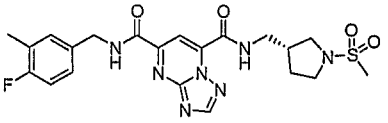
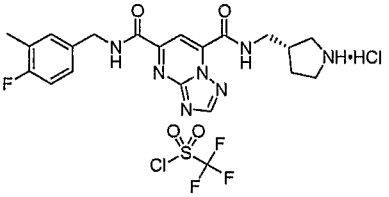
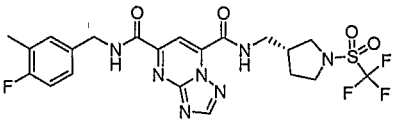
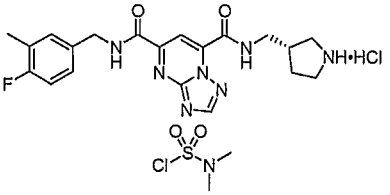
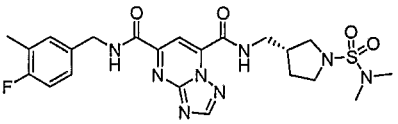
To a suspension of the title compound from the Example 296, Step B (23.8 mg) in dry CH_2Cl_2 (1 mL) were added a 1M solution of acetyl chloride in dry CH_2Cl_2 (50 μL) and $^iPr_2NEt$ (26.1 μL). The reaction mixture was stirred at room temperature for 1 h, concentrated and purified by flash chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a beige/white solid (24.1 mg, >99%). $[MH]^+ = 482$.

Examples 300-309

[0564] Following a similar procedure as described in the Example 299, except using the amines and the acid chlorides indicated in Table II-4 below, the following compounds were prepared.

Table II-4

Ex. #	amine, acid chloride	product	yield
300			92% $[MH]^+ = 524$
301			99% $[MH]^+ = 518$
302			73% $[MH]^+ = 468$
303			75% $[MH]^+ = 504$

Ex. #	amine, acid chloride	product	yield
304			97% $[MH]^+ = 454$
305			94% $[MH]^+ = 490$
306			89% $[MH]^+ = 454$
307			95% $[MH]^+ = 490$
308			71% $[MH]^+ = 544$
309			83% $[MH]^+ = 519$

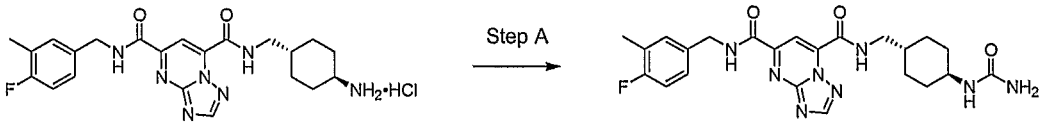
Example 310



[0565] Step A

To a solution of the title compound from the Example 298(a) (22.4 mg) in dry CH_2Cl_2 (500 μL) were added $^iPr_2NEt$ (17.4 μL) and sulfamide (10.8 mg). The resulting reaction mixture was heated in a sealed tube to 140°C (microwave) for 2 h, concentrated and purified by flash chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (11.7 mg, 48%). $[MH]^+ = 491$.

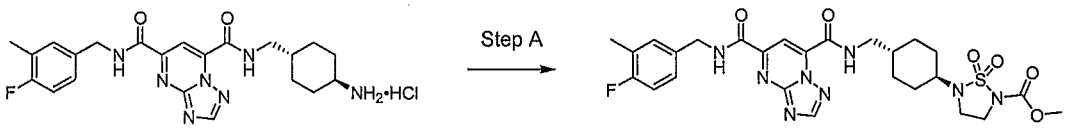
Example 311



[0566] Step A

To a suspension of the title compound from the Example 296, Step B (23.8 mg) in dry CH_2Cl_2 (500 μL) was added KO^tBu (6.4 mg). The resulting reaction mixture was stirred at room temperature for 5 min, then ^iPrOH (50 μL) and trimethylsilyl isocyanate (13.9 μL) were added and stirring at room temperature was continued for 19 h. The mixture was diluted with MeOH (5 mL), concentrated and purified by flash chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (15 mg, 62%). $[MH]^+ = 483$.

Example 312



[0567] Step A

To a solution of the title compound from the Example 296, Step B (20 mg) in DMF (2.5 mL) were successively added $^iPr_2NEt$ (15 μL) and 2-iodoethanol (3.5 μL). Using a microwave, the mixture was heated in a sealed vial at 100°C for 10 min. The mixture was concentrated and dissolved in dry THF (1 mL). Methyl *N*-(triethylammoniosulfonyl) carbamate ["Burgess reagent"] (27 mg) was added and using a microwave, the mixture was heated in a sealed vial at 130°C for 7 min. Concentration and purification by chromatography

(silica, CH_2Cl_2/MeOH) afforded the title compound as a colorless solid (1.7 mg, 6%). $[MH]^+ = 603$.

Example 313



[0568] Step A

To a suspension of the title compound from the Example 297 (23.1 mg) in dry CH_2Cl_2 (500 μL) was added KO^{t}Bu (6.4 mg). The resulting reaction mixture was stirred at room temperature for 5 min, then ^{i}PrOH (50 μL) and trimethylsilyl isocyanate (13.9 μL) were added and stirring at room temperature was continued for 16 h. The mixture was diluted with MeOH (5 mL), concentrated and purified by flash chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound (10 mg, 43%). $[MH]^+ = 469$.

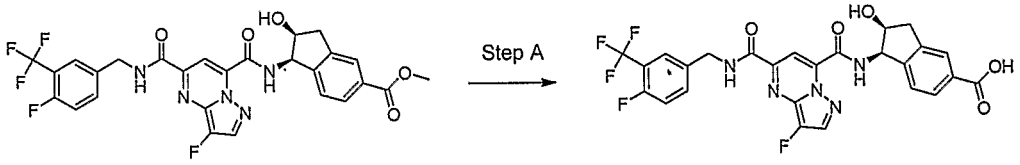
Example 314



[0569] Step A

To a solution of the title compound from the Example 25 (43.9 mg) in THF (10 mL) was added a solution of LiOH (18 mg) in H_2O (10 mL). The solution was stirred for 5 h, acidified, concentrated and purified by preparative thin layer chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a bright yellow solid (16.4 mg, 38%). $[MH]^+ = 488$.

Example 315



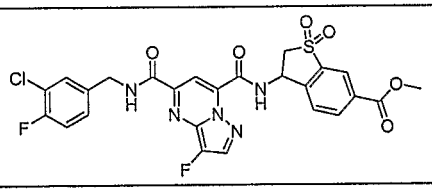
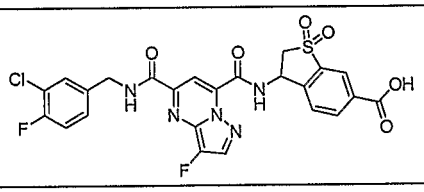
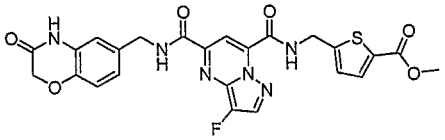
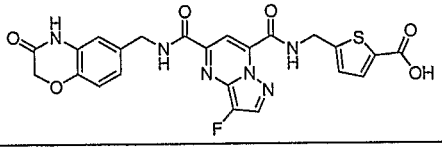
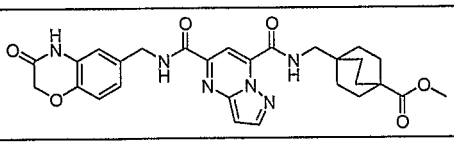
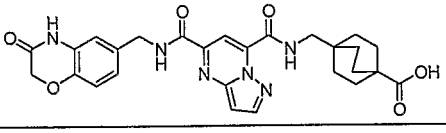
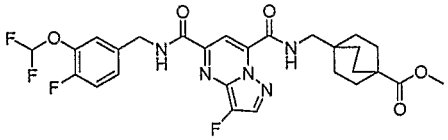
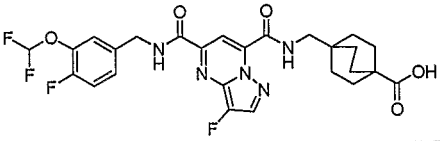
[0570] Step A

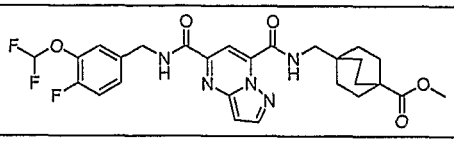
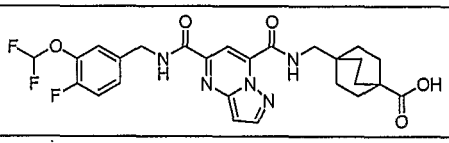
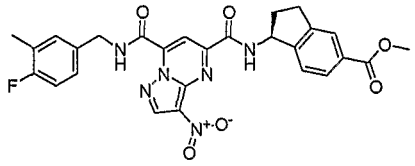
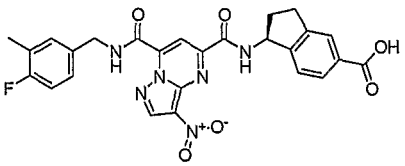
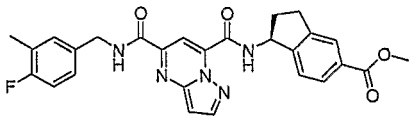
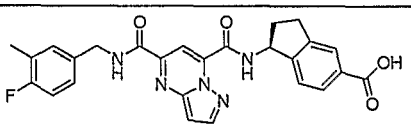
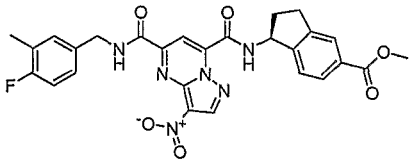
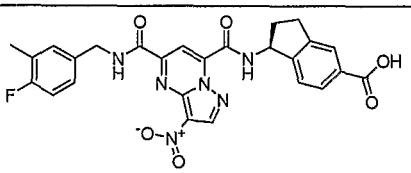
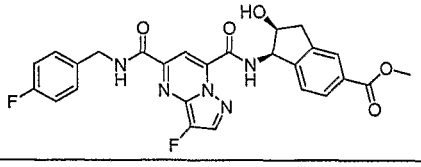
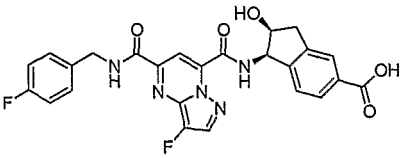
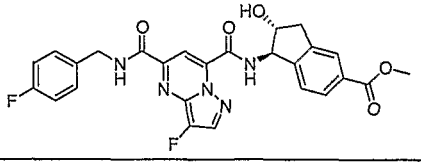
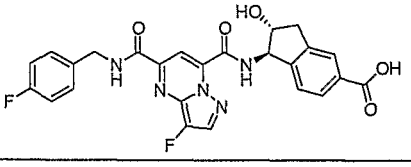
Using a microwave, a mixture of the title compound from the Example 5 (51 mg) and trimethyltin hydroxide (236 mg) in 1,2-dichloroethane (2 mL) in a sealed vial was stirred at 160°C for 1 h. The contents were loaded onto a silica and purified by chromatography (silica, CH_2Cl_2/MeOH) to give a yellow solid (18 mg, 35%). $[M-H]^- = 574$.

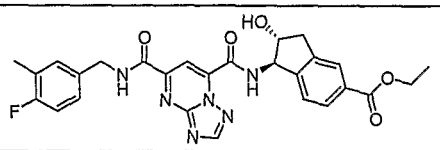
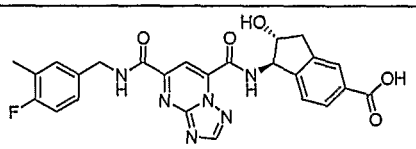
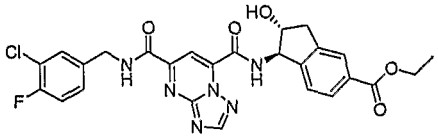
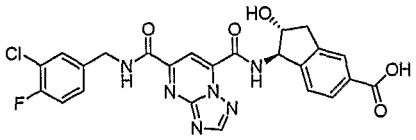
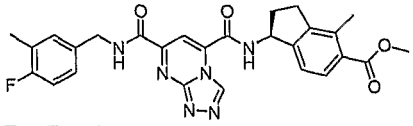
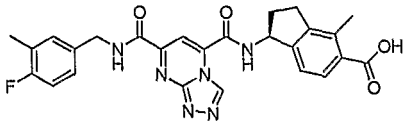
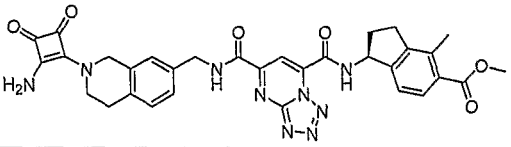
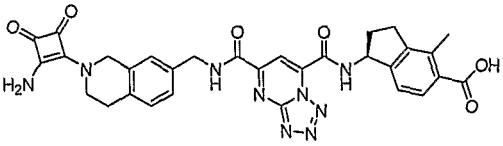
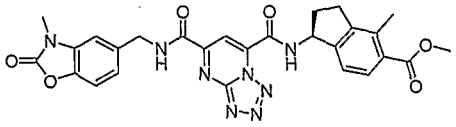
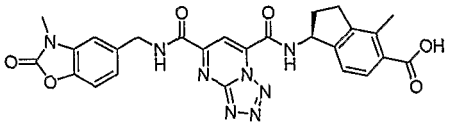
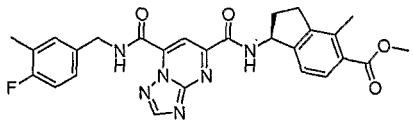
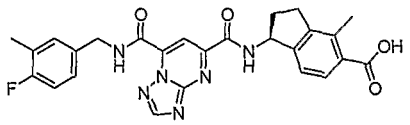
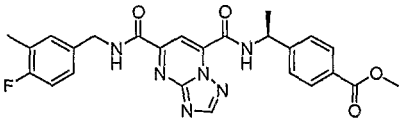
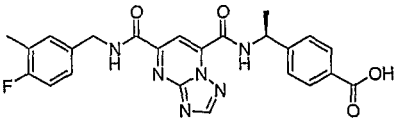
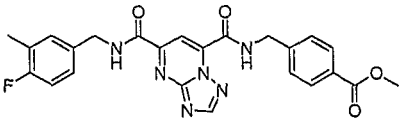
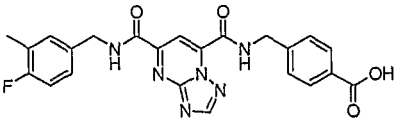
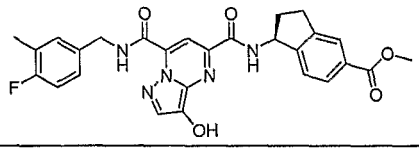
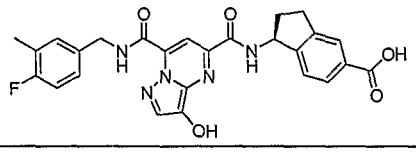
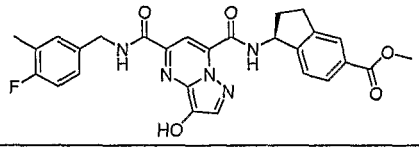
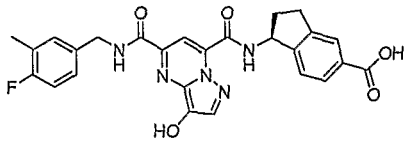
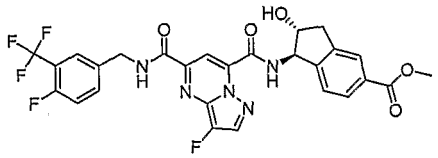
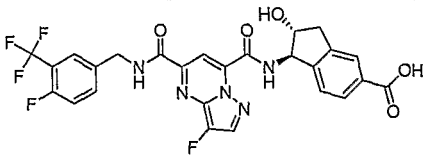
Examples 316-361

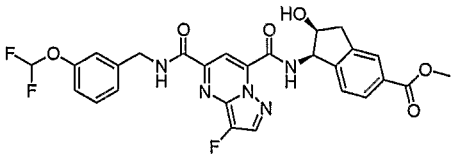
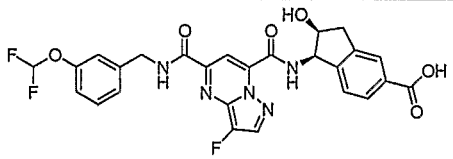
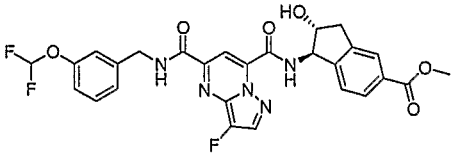
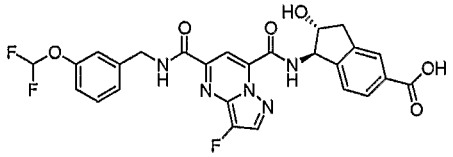
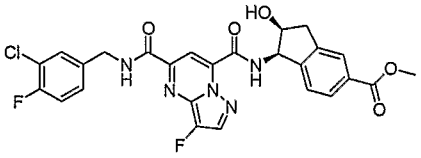
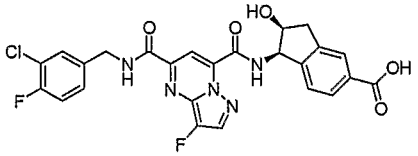
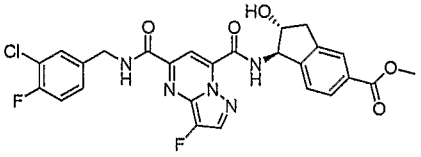
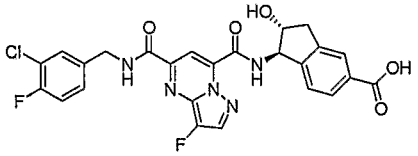
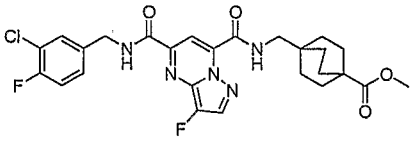
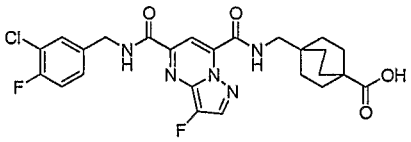
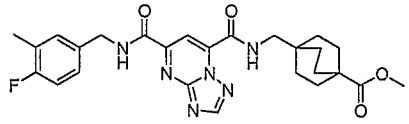
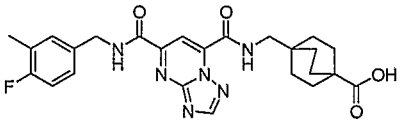
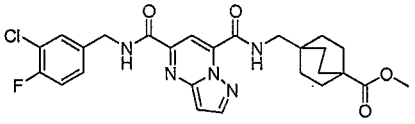
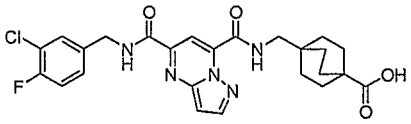
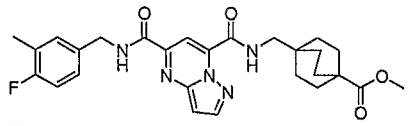
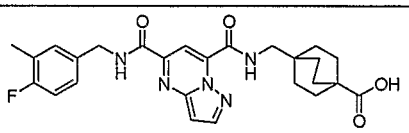
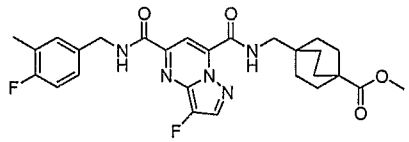
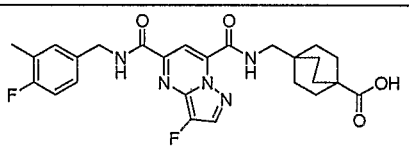
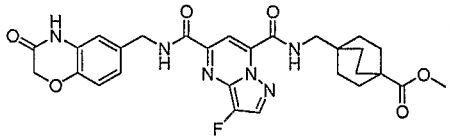
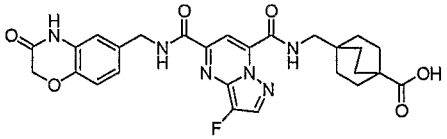
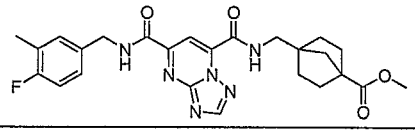
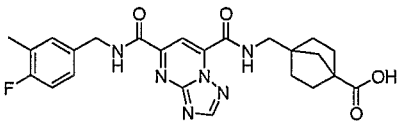
[0571] Following similar procedures as described in the Examples 314 (method A) or 315 (method B), except using the esters indicated in Table II-5 below, the following compounds were prepared.

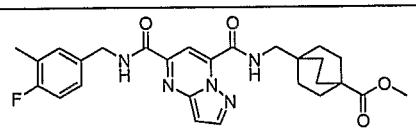
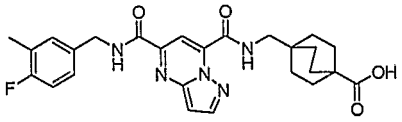
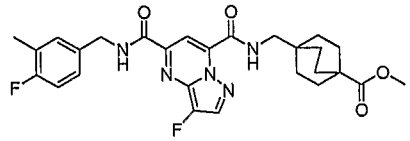
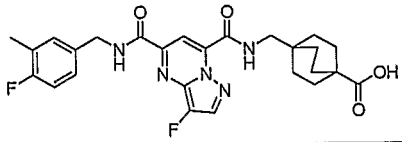
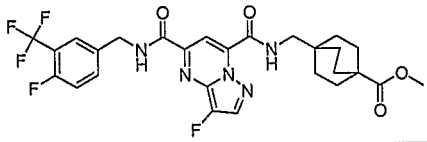
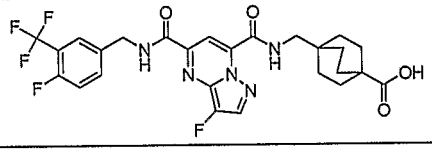
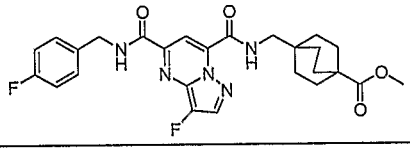
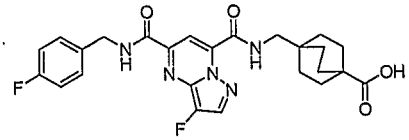
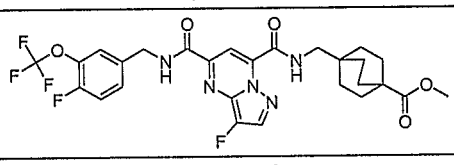
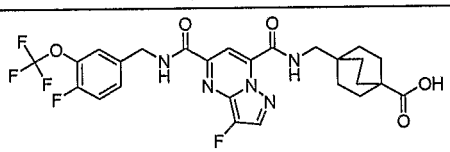
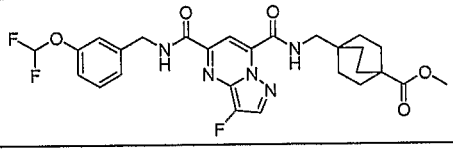
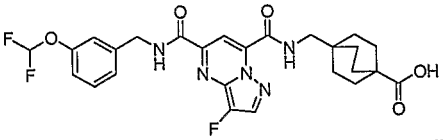
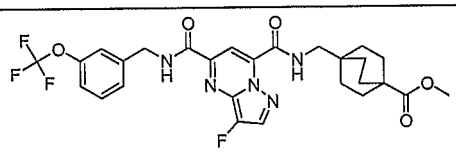
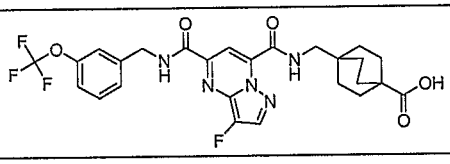
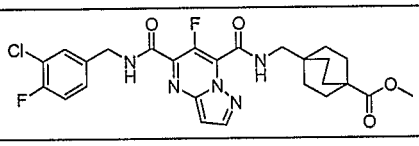
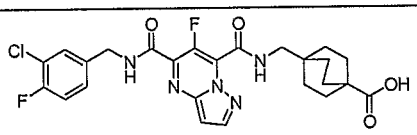
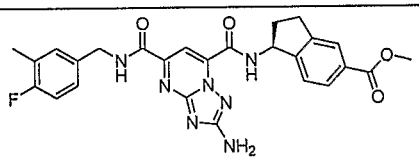
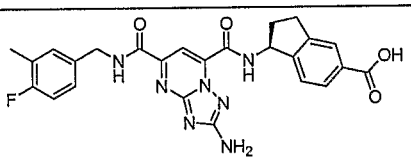
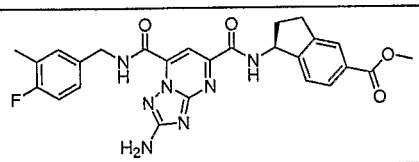
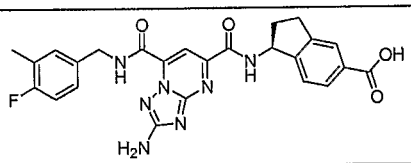
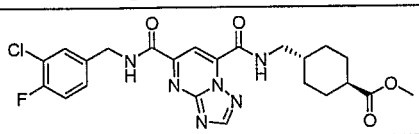
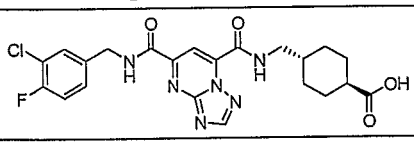
Table II-5

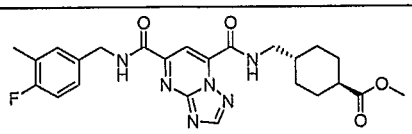
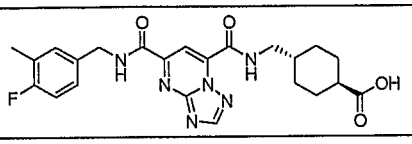
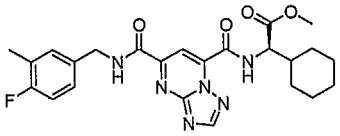
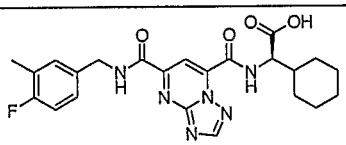
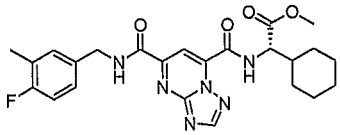
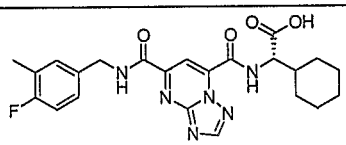
Ex. #	ester	product	method, yield
316			A, 60% $[MH]^+ = 576$
317			A, 8% $[MH]^+ = 525$
318			B, 40% $[MH]^+ = 533$
319			B, 54% $[MH]^+ = 564$

Ex. #	ester	product	method, yield
320			B, 40% $[MH]^+ = 546$
321			A, 40% ^{1}H-NMR ($CDCl_3$) δ = 10.50 (br d, 1 H), 9.00 (s, 1 H), 8.90 (s, 1 H), 8.25 (d, 1 H), 7.95 (s, 1 H), 7.90 (d, 1 H), 7.35 (d, 1 H), 7.25-7.10 (m, 2 H), 7.00 (m, 1 H), 5.75 (m, 1 H), 4.70 (d, 2 H), 3.20-2.80 (m, 3 H), 2.25 (s, 3 H), 2.25-2.00 (m, 1 H).
322			A, 31% $[MH]^+ = 488$
323			A, 37% $[MH]^+ = 533$
324			B, 66% $[M-H]^- = 506$
325			B, 71% $[M-H]^- = 506$

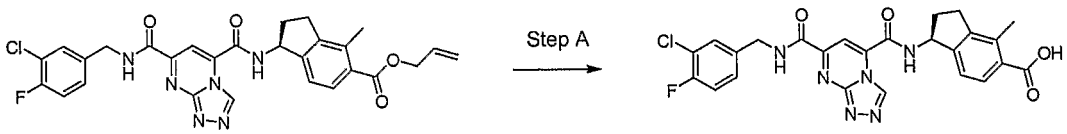
Ex. #	ester	product	method, yield
326			B, 70% $[M-H]^-$ = 531
327			B, 82% $[M-H]^-$ = 522
328			B, 45% $[MH]^+$ = 503
329			B, 18% $[MH]^+$ = 622
330			B, 15% $[MH]^+$ = 543
331			B, 14% $[M-H]^-$ = 501
332			B, 50% $[MH]^+$ = 477
333			B, 32% $[MH]^+$ = 463
334			A, 86% $[MH]^+$ = 504
335			A, 51% $[MH]^+$ = 504
336			B, 34% $[M-H]^-$ = 574

Ex. #	ester	product	method, yield
337			B, 46% $[M-H]^-$ = 554
338			B, 29% $[M-H]^-$ = 554
339			B, 45% $[M-H]^-$ = 540
340			B, 44% $[M-H]^-$ = 540
341			B, 52% $[MH]^+$ = 532
342			B, 42% $[MH]^+$ = 495
343			B, 40% $[MH]^+$ = 514
344			B, 35% $[MH]^+$ = 494
345			B, 43% $[MH]^+$ = 512
346			B, 39% $[MH]^+$ = 551
347			B, 21% $[MH]^+$ = 481

Ex. #	ester	product	method, yield
348			B, 41% $[MH]^+ = 498$
349			B, 39% $[MH]^+ = 516$
350			B, 32% $[MH]^+ = 566$
351			B, 37% $[MH]^+ = 498$
352			B, 44% $[MH]^+ = 582$
353			B, 42% $[MH]^+ = 546$
354			B, 46% $[MH]^+ = 564$
355			B, 15% $[MH]^+ = 532$
356			A, 11% $[MH]^+ = 504$
357			B, 10% $[MH]^+ = 504$
358			B, 68% $[MH]^+ = 489$

Ex. #	ester	product	method, yield
359			B, 66% $[MH]^+ = 469$
360			B, 94% $[MH]^+ = 469$
361			B, 95% $[MH]^+ = 469$

Example 362



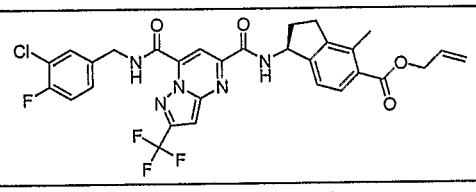
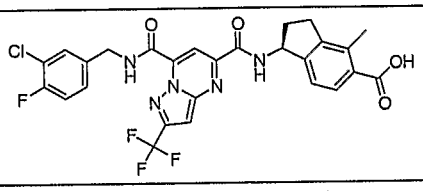
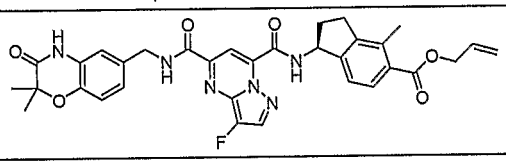
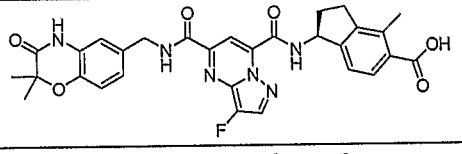
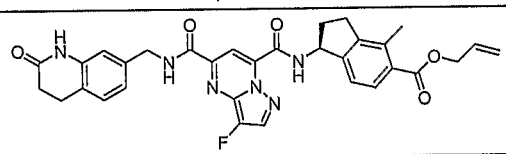
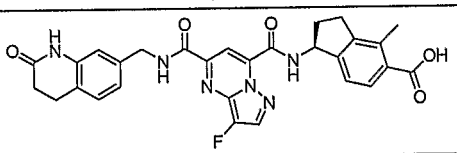
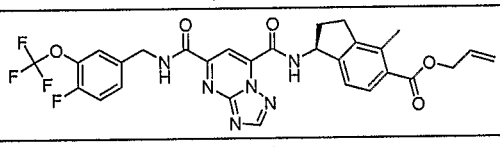
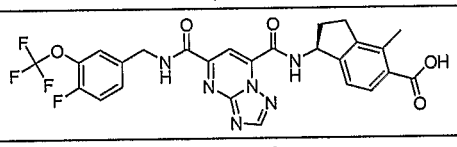
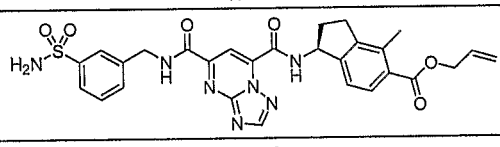
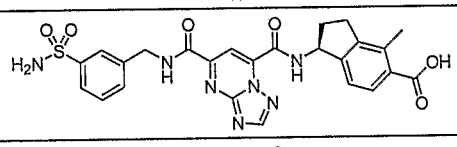
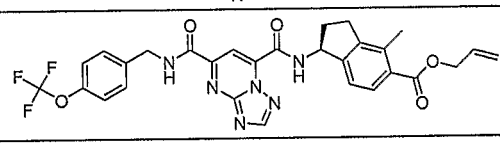
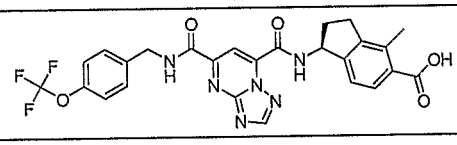
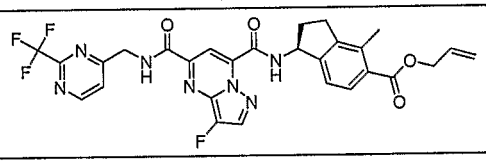
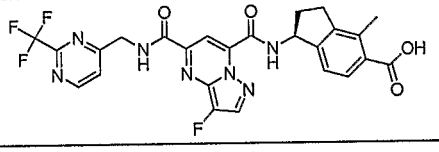
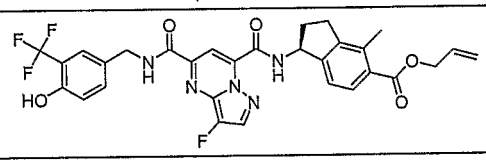
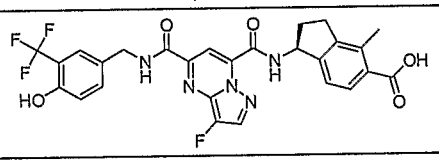
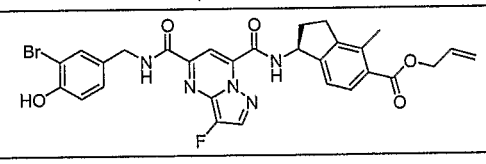
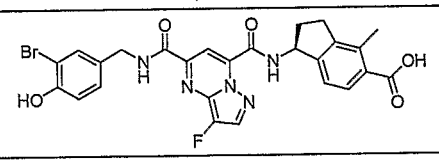
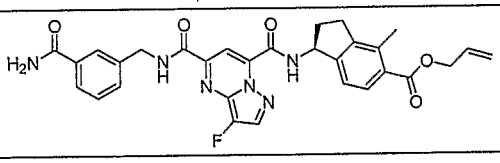
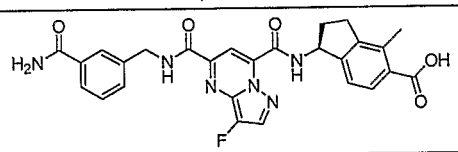
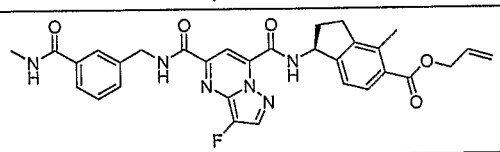
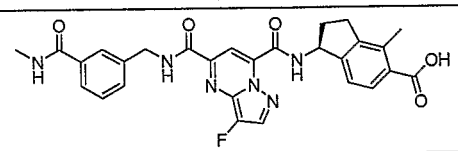
[0572] Step A

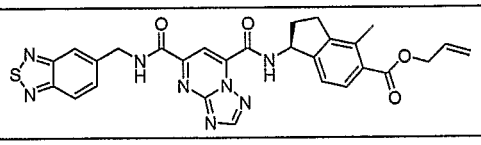
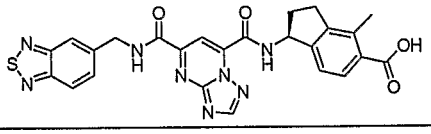
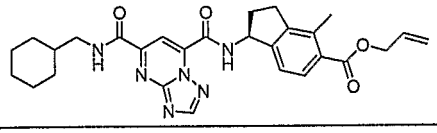
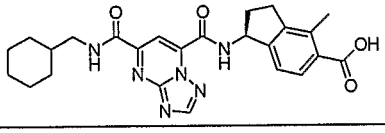
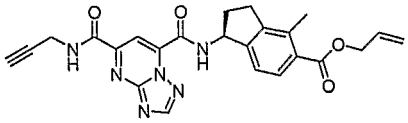
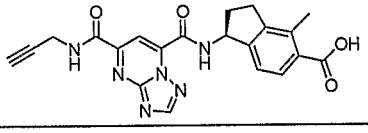
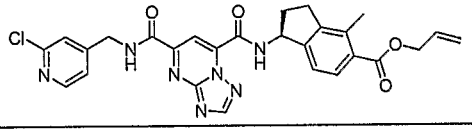
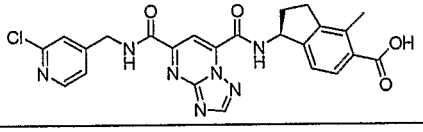
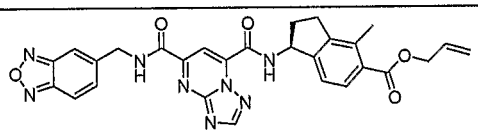
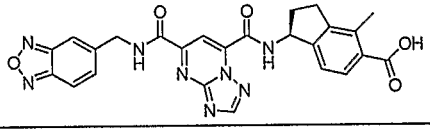
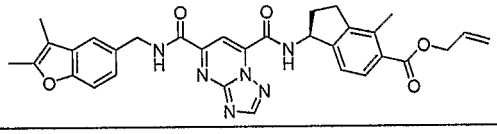
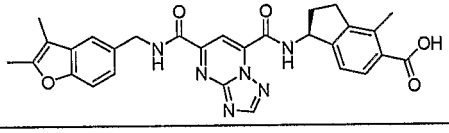
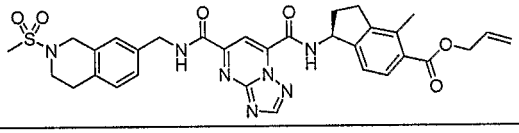
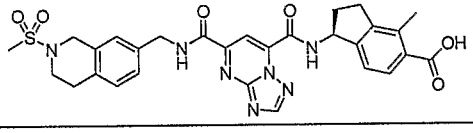
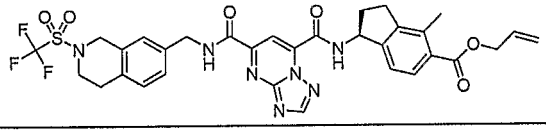
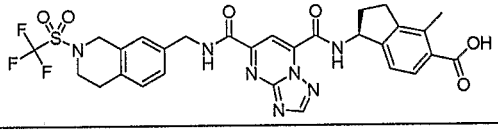
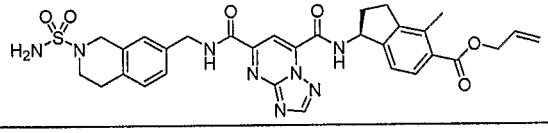
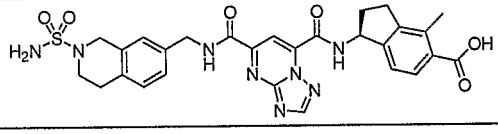
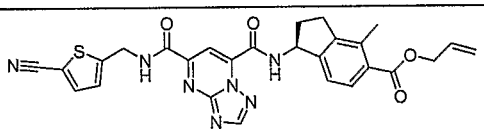
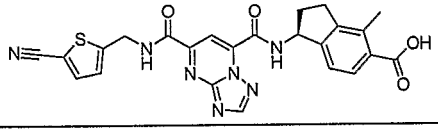
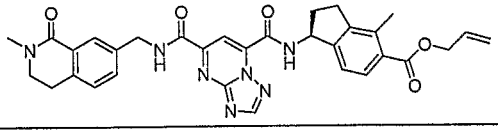
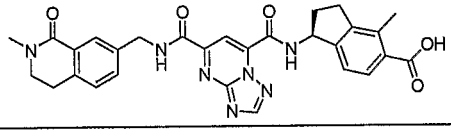
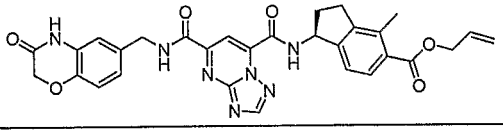
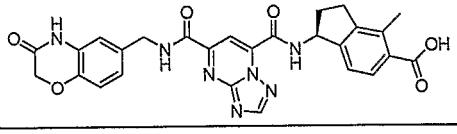
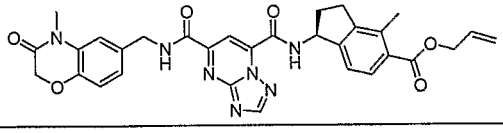
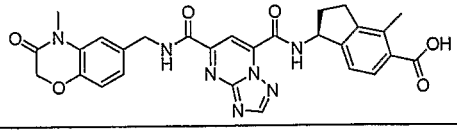
To a solution of the title compound from the Example 184 (109 mg) in THF (4 mL) were added morpholine (0.17 mL) and $Pd(PPh_3)_4$ (23.8 mg). The mixture was stirred at room temperature for 3½ h, diluted with a 4M solution of HCl in 1,4-dioxane (490 μL) and concentrated. The remaining residue was purified by chromatography (silica, CH_2Cl_2/MeOH) and preparative thin layer chromatography (silica, CH_2Cl_2/MeOH) to give the title compound as a yellow solid (39.4 mg, 39%). $[M-H]^- = 521$.

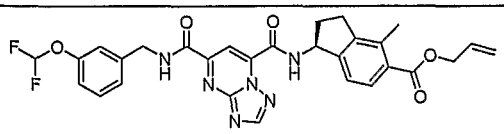
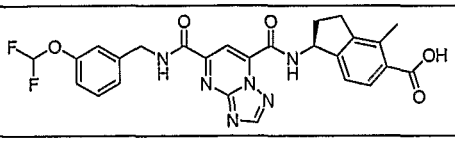
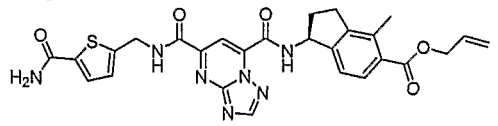
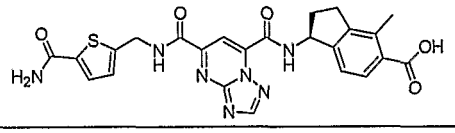
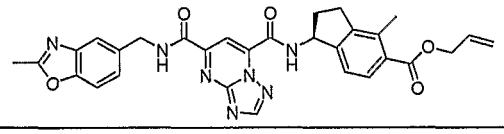
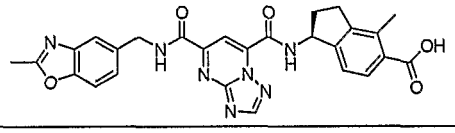
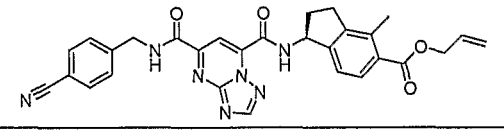
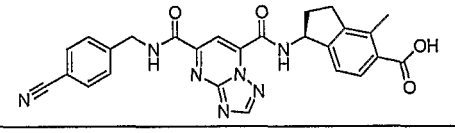
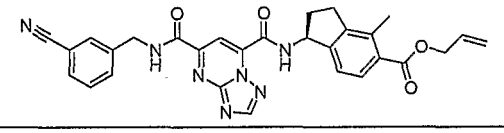
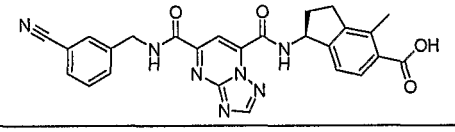
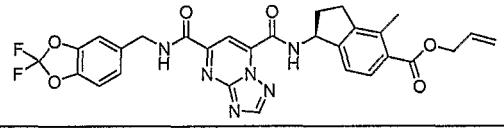
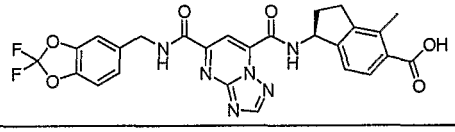
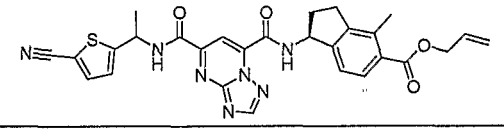
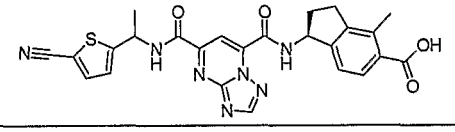
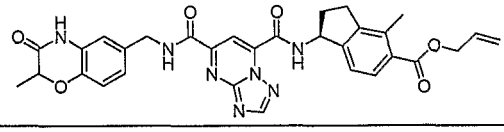
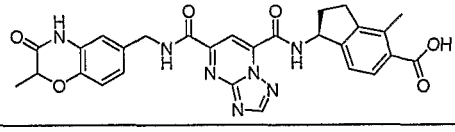
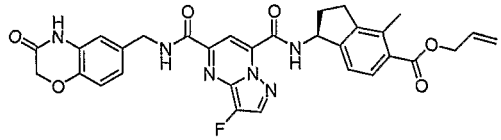
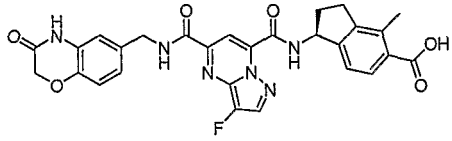
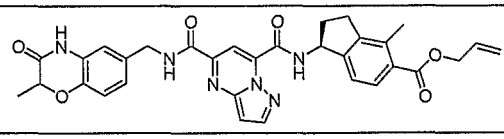
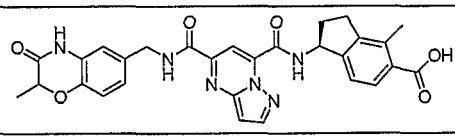
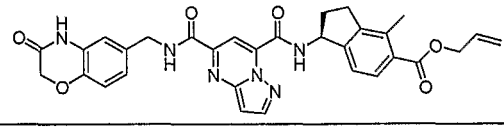
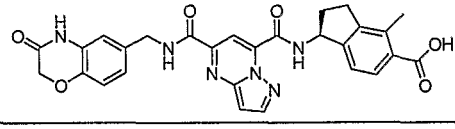
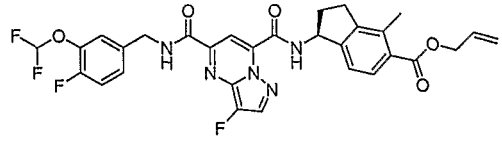
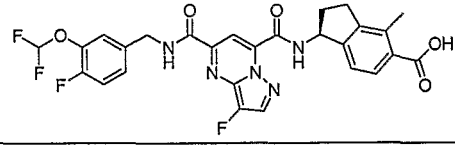
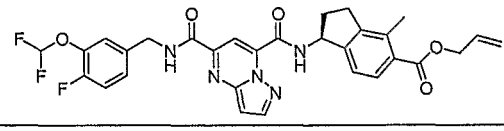
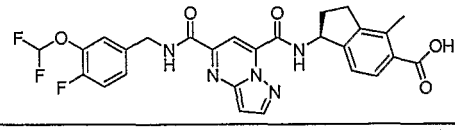
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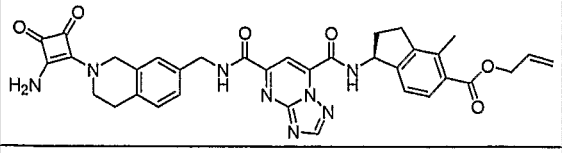
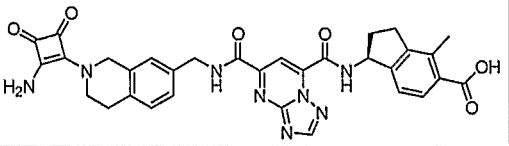
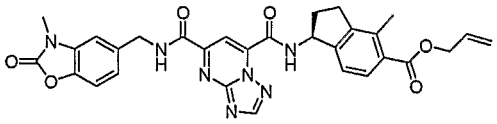
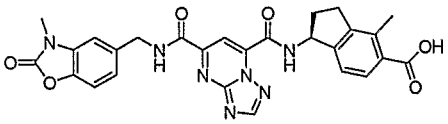
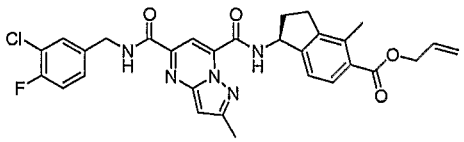
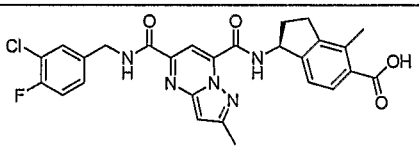
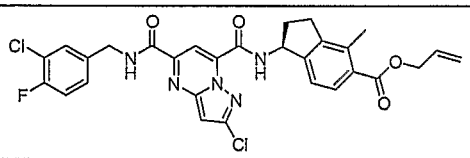
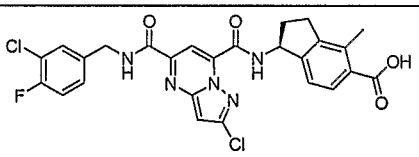
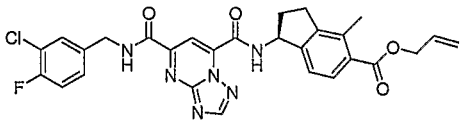
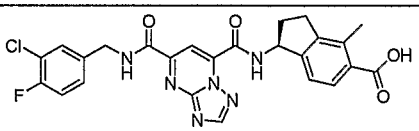
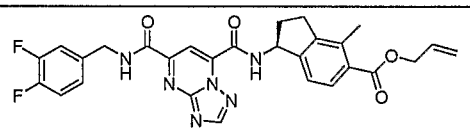
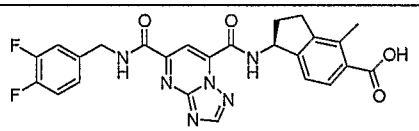
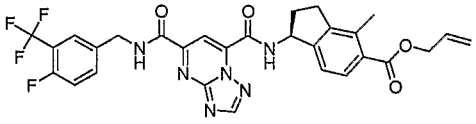
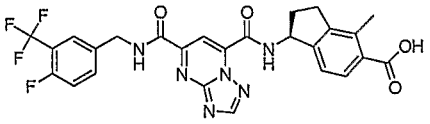
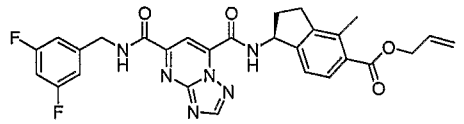
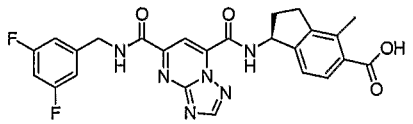
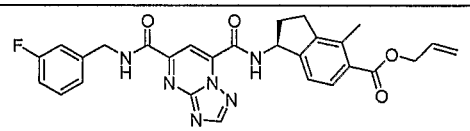
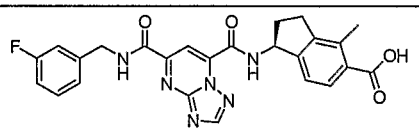
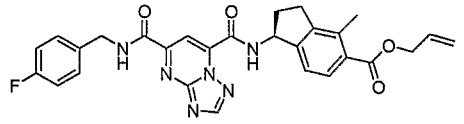
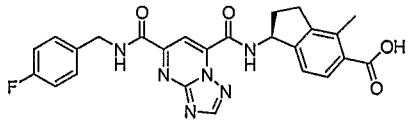
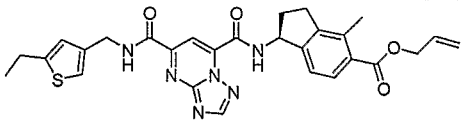
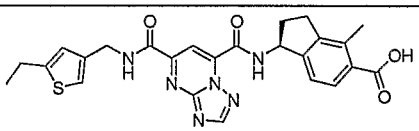
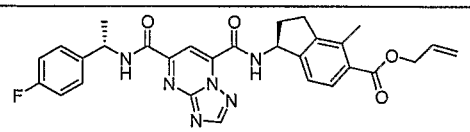
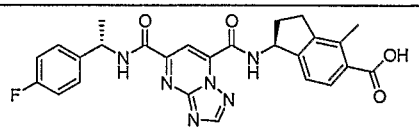
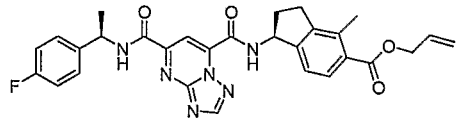
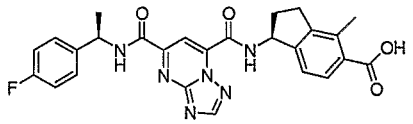
[0573] Following a similar procedure as described in the Example 362, except using the esters indicated in Table II-6 below, the following compounds were prepared.

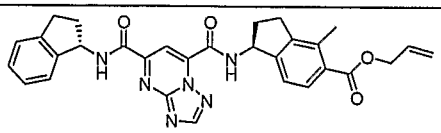
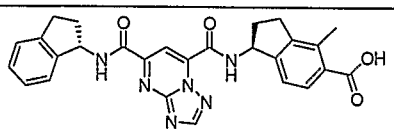
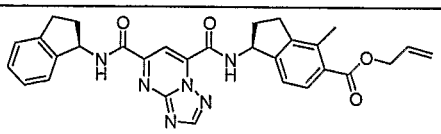
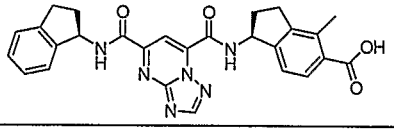
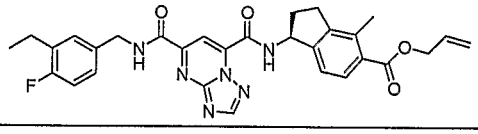
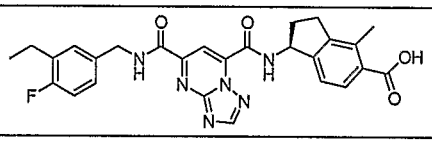
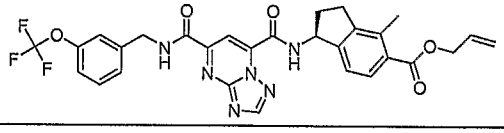
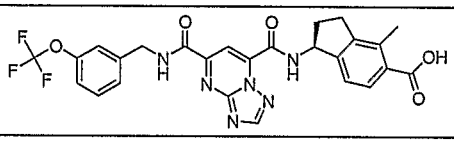
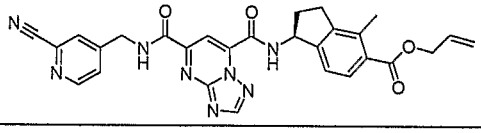
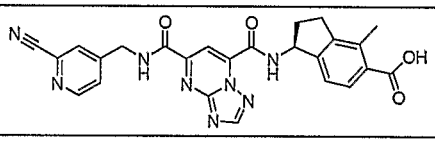
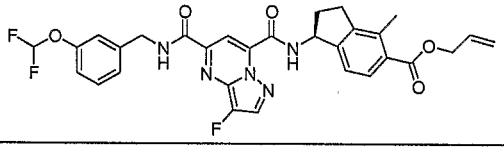
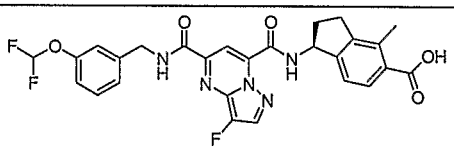
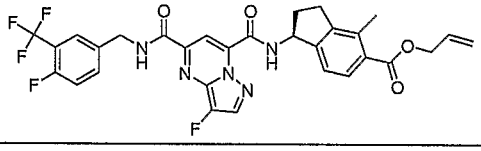
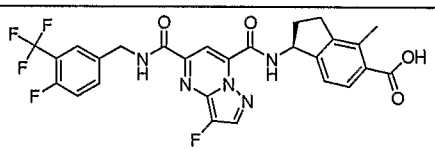
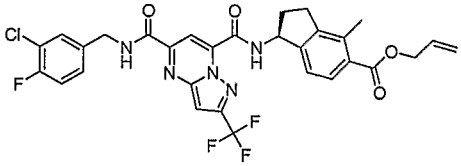
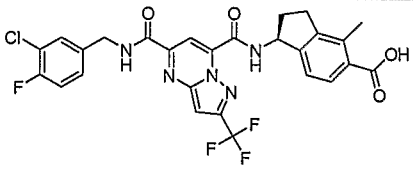
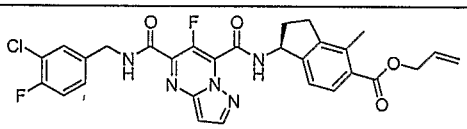
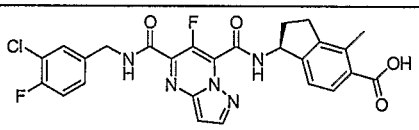
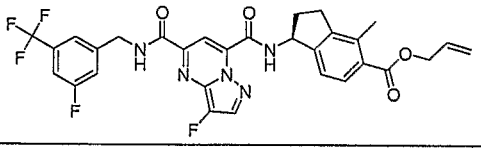
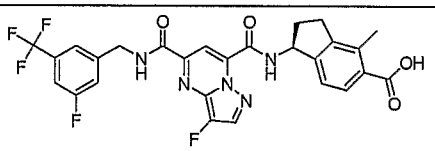
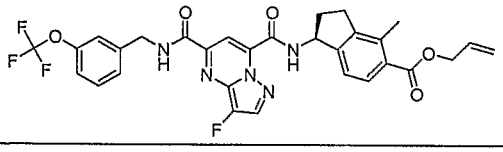
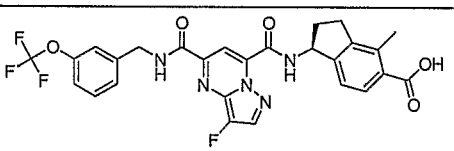
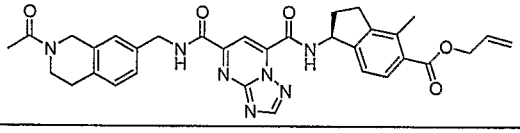
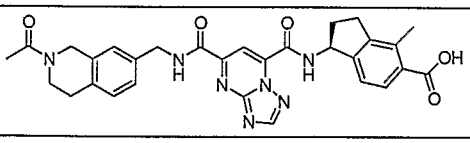
Table II-6

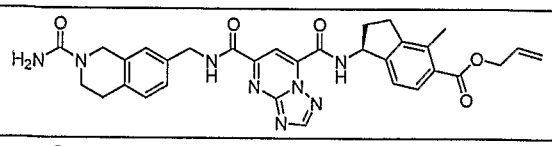
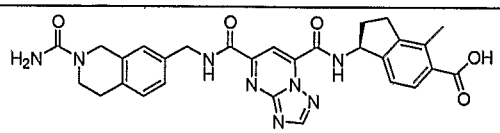
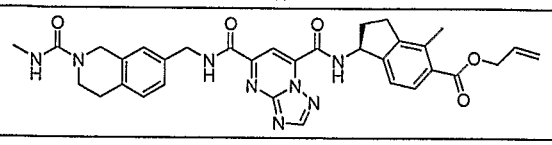
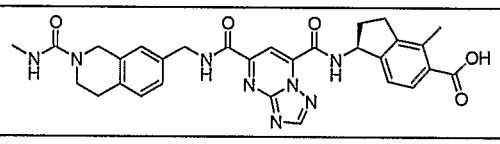
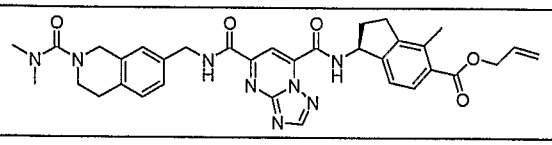
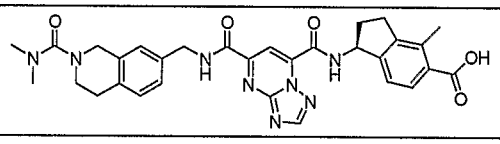
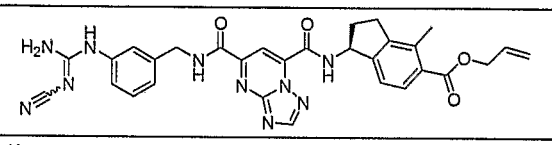
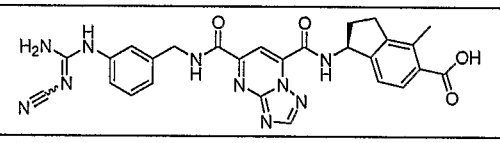
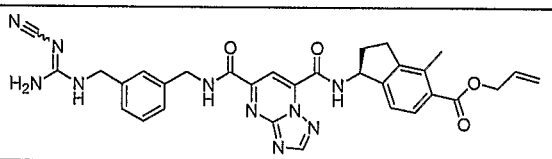
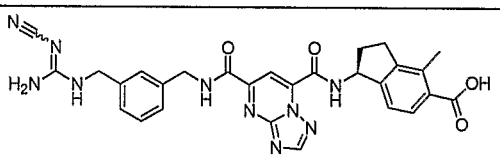
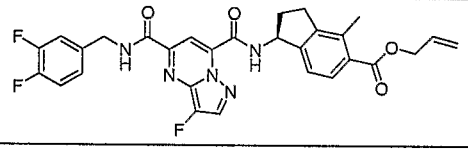
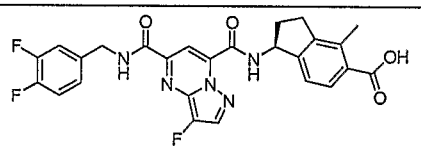
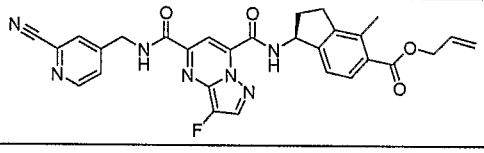
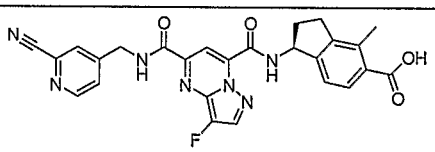
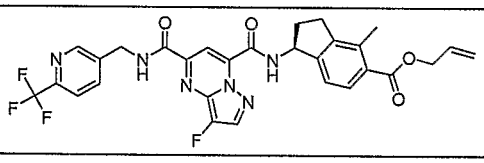
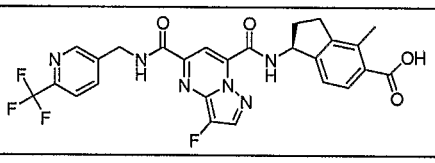
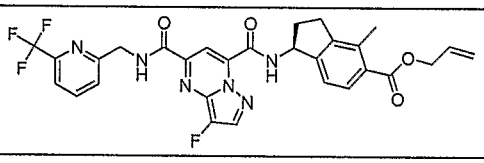
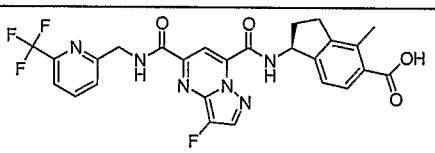
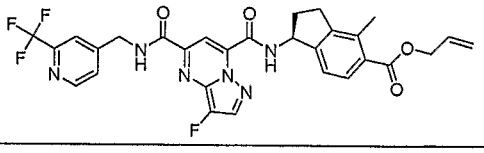
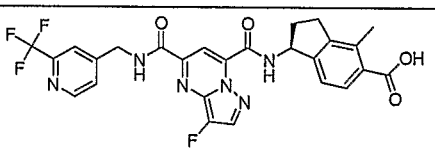
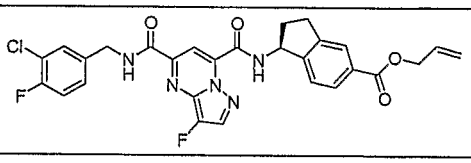
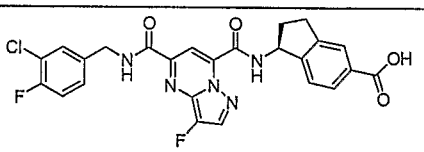
Ex. #	ester	product	yield
363			53% $[M-H]^-$ = 588
364			n.d. $[MH]^+$ = 609
365			n.d. $[MH]^+$ = 557
366			42% $[MH]^+$ = 573
367			42% (over 2 steps) $[MH]^+$ = 550
368			37% $[MH]^+$ = 555
369			48% $[MH]^+$ = 558
370			90% $[MH]^+$ = 572
371			49% $[MH]^+$ = 583
372			59% $[MNa]^+$ = 553
373			40% $[MNa]^+$ = 567

Ex. #	ester	product	yield
374			37% (over 2 steps) $[MH]^+ = 529$
375			20% (over 2 steps) $[MH]^+ = 477$
376			34% (over 2 steps) $[MH]^+ = 419$
377			29% (over 2 steps) $[MH]^+ = 506$
378			90% $[MH]^+ = 579$
379			90% $[MH]^+ = 579$
380			41% $[MH]^+ = 604$
381			77% $[MH]^+ = 658$
382			71% $[MH]^+ = 605$
383			67% $[MH]^+ = 502$
384			75% $[MH]^+ = 554$
385			18% $[MH]^+ = 542$
386			62% $[MH]^+ = 556$

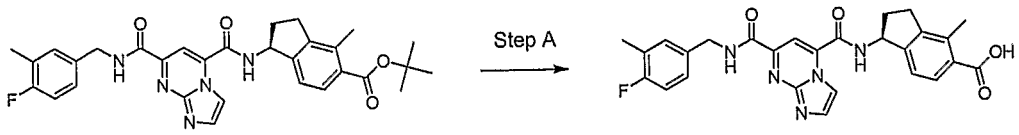
Ex. #	ester	product	yield
387			33% $[MH]^+ = 537$
388			69% $[MH]^+ = 520$
389			22% $[MH]^+ = 526$
390			8% $[MH]^+ = 496$
391			77% $[MH]^+ = 496$
392			71% $[MH]^+ = 551$
393			65% $[MH]^+ = 516$
394			46% $[MH]^+ = 556$
395			98% $[MH]^+ = 559$
396			80% $[MH]^+ = 554$
397			58% $[MH]^+ = 541$
398			90% $[MH]^+ = 572$
399			95% $[MH]^+ = 554$

Ex. #	ester	product	yield
400			77% $[MH]^+ = 621$
401			68% $[MH]^+ = 542$
402			86% $[MH]^+ = 536$
403			87% $[MH]^+ = 556$
404			50% $[MH]^+ = 524$
405			45% $[MH]^+ = 507$
406			30% (over 2 steps) $[MH]^+ = 557$
407			n.d. $[MH]^+ = 507$
408			90% $[MH]^+ = 489$
409			78% $[MH]^+ = 489$
410			86% $[MH]^+ = 505$
411			57% (over 2 steps) $[MH]^+ = 503$
412			57% (over 2 steps) $[MH]^+ = 503$

Ex. #	ester	product	yield
413			20% (over 2 steps) $[MH]^+ = 497$
414			29% (over 2 steps) $[MH]^+ = 497$
415			36% (over 2 steps) $[MH]^+ = 517$
416			19% (over 2 steps) $[MH]^+ = 555$
417			7% (over 2 steps) $[MH]^+ = 497$
418			82% (over 2 steps) $[MH]^+ = 554$
419			82% (over 2 steps) $[MH]^+ = 614$
420			40% $[M-H]^- = 588$
421			60% $[MH]^+ = 540$
422			94% $[MH]^+ = 574$
423			98% $[MH]^+ = 572$
424			45% $[MH]^+ = 568$

Ex. #	ester	product	yield
425			20% $[MH]^+ = 569$
426			51% $[MH]^+ = 583$
427			15% $[MH]^+ = 597$
428			24% $[MH]^+ = 553$
429			31% $[MH]^+ = 567$
430			>99% $[MH]^+ = 524$
431			46% $[MH]^+ = 514$
432			64% $[MH]^+ = 557$
433			78% $[MH]^+ = 557$
434			65% $[MH]^+ = 557$
435			71% $[MH]^+ = 526$

Example 436



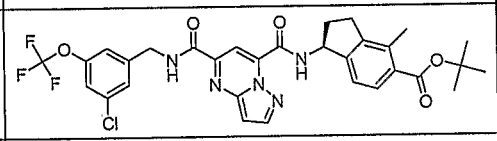
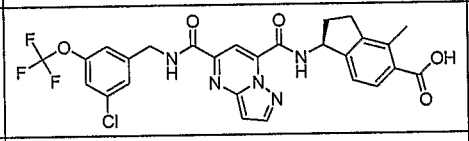
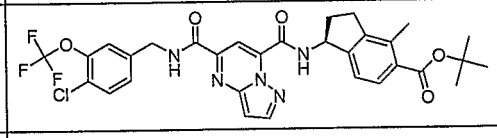
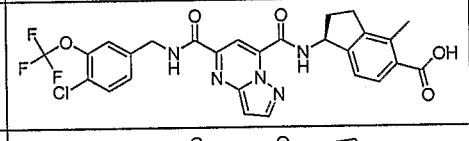
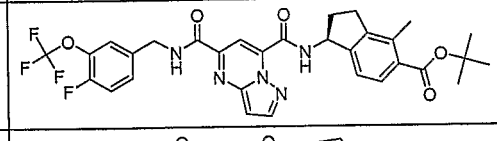
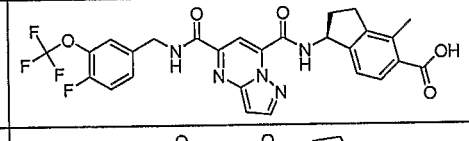
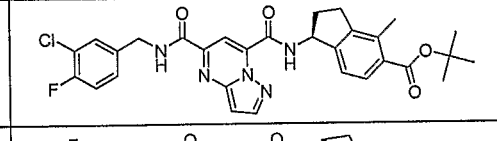
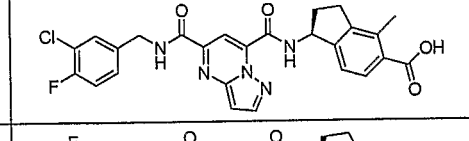
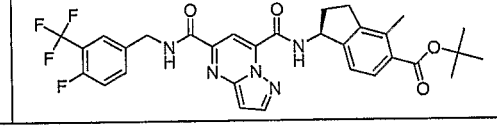
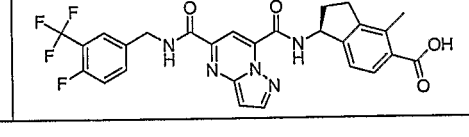
[0574] Step A

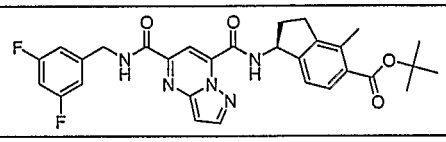
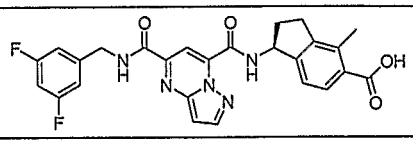
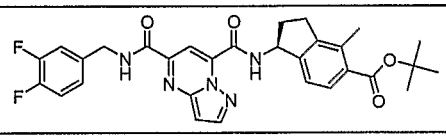
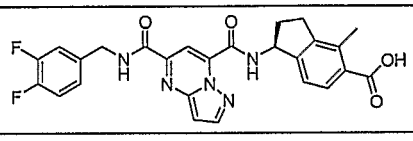
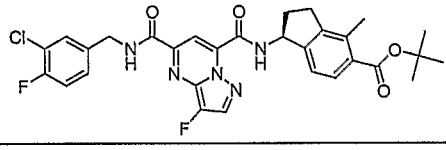
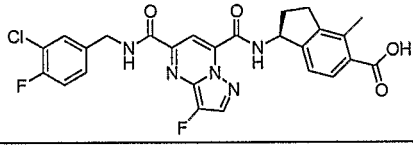
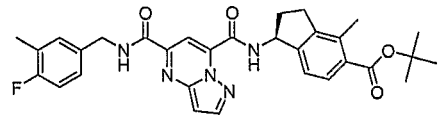
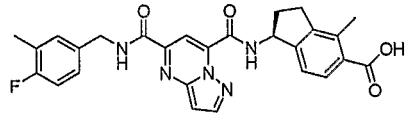
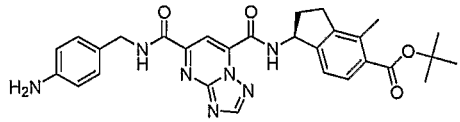
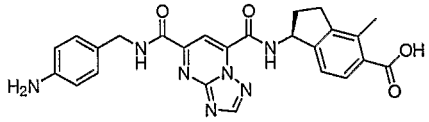
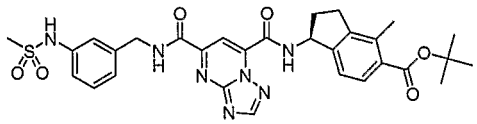
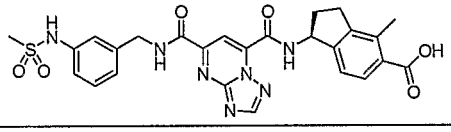
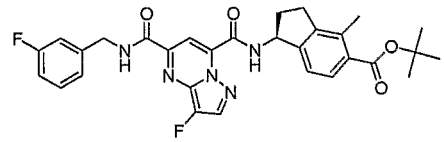
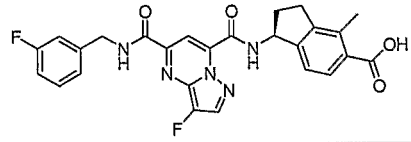
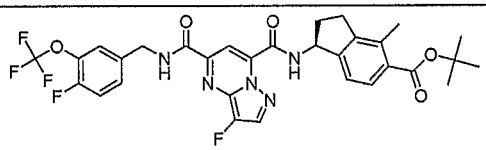
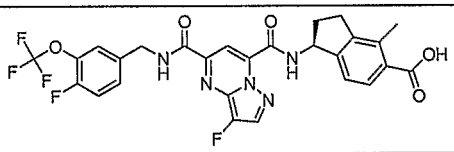
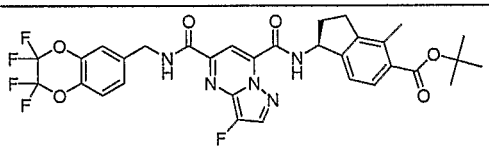
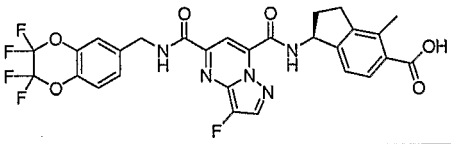
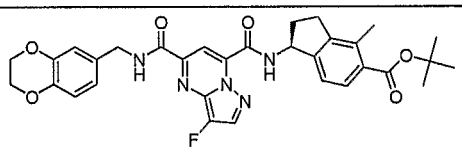
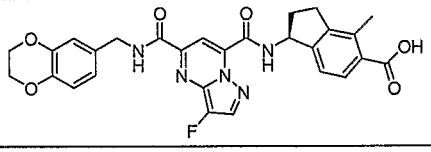
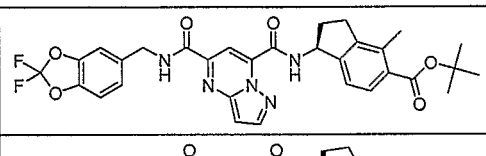
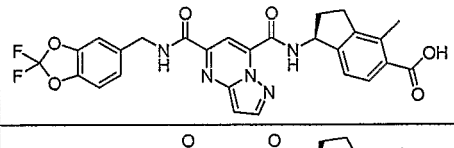
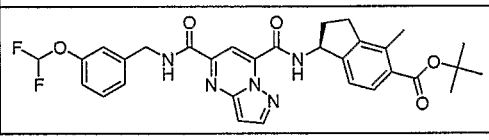
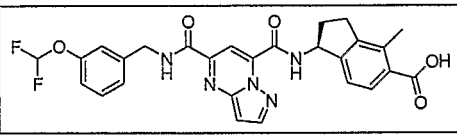
A solution of the title compound from the Example 83 (20 mg) in a mixture of trifluoroacetic acid (100 μL) and CH_2Cl_2 (100 μL) was stirred for 30 min and then concentrated. The remaining residue was washed with Et_2O (200 μL) to give a yellow solid (17 mg, 92%). $[MH]^+ = 502$.

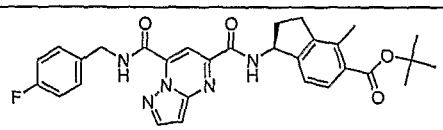
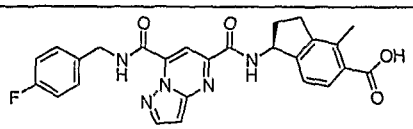
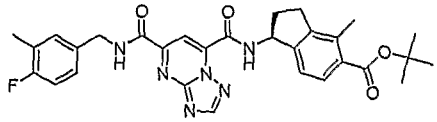
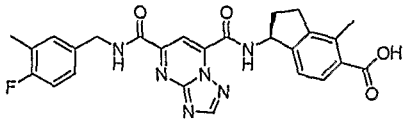
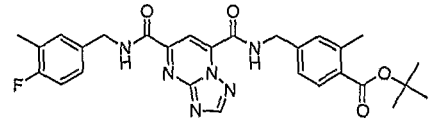
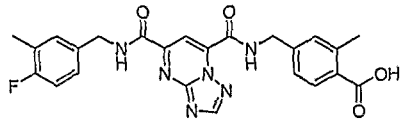
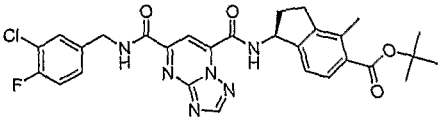
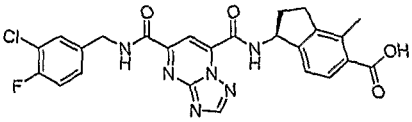
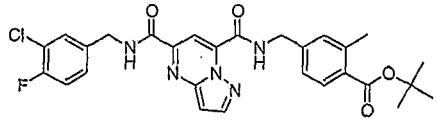
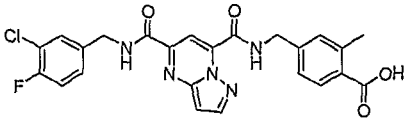
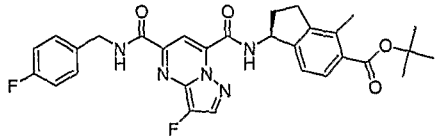
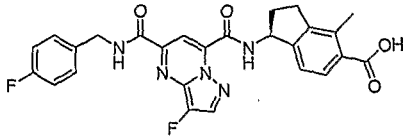
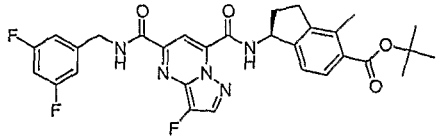
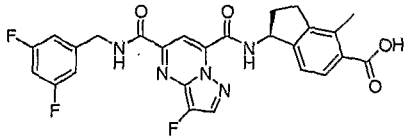
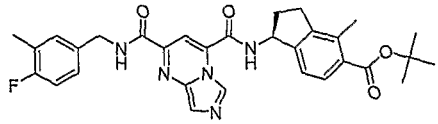
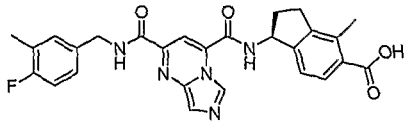
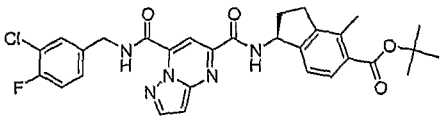
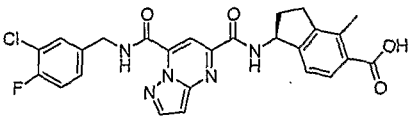
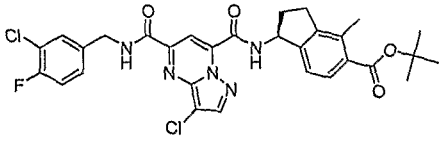
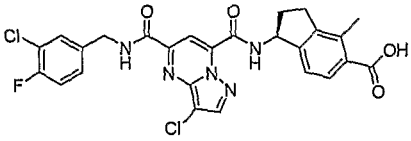
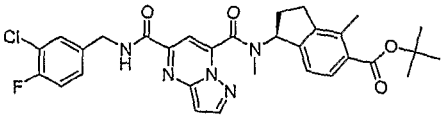
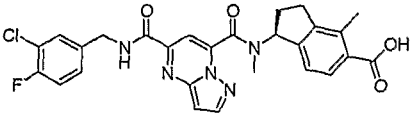
Examples 437-464

[0575] Following a similar procedure as described in the Example 436, except using the esters as indicated in Table II-7 below, the following compounds were prepared.

Table II-7

Ex. #	ester	product	yield
437			n.d. $[M-H]^- = 586$
438			n.d. $[M-H]^- = 586$
439			95% $[MH]^+ = 572$
440			89% $[MH]^+ = 522$
441			98% $[MH]^+ = 556$

Ex. #	ester	product	yield
442			35% $[MH]^+ = 506$
443			98% $[MH]^+ = 506$
444			96% $[MH]^+ = 540$
445			74% $[MH]^+ = 502$
446			96% $[MH]^+ = 486$
447			79% $[M-H]^- = 562$
448			56% (over 2 steps) $[MH]^+ = 506$
449			63% (over 2 steps) $[MH]^+ = 590$
450			32% (over 2 steps) $[MH]^+ = 618$
451			10% (over 2 steps) $[MH]^+ = 546$
452			90% $[MH]^+ = 550$
453			90% $[MH]^+ = 536$

Ex. #	ester	product	yield
454			73% $[M-H]^-$ = 488
455			53% $[M-H]^-$ = 501
456			36% $[MH]^+$ = 477
457			50% $[MH]^+$ = 523
458			50% $[MH]^+$ = 496
459			67% (over 2 steps) $[MH]^+$ = 506
460			65% (over 2 steps) $[MH]^+$ = 524
461			56% $[MH]^+$ = 502
462			83% $[M-H]^-$ = 520
463			>99% $[MH]^+$ = 556
464			>99% $[M-"indene"]^+$ = 362

Example 465



[0576] Step A

To a solution of the title compound from the Example 360 (50 mg) in THF (1.5 mL) was added *N,N'*-carbonyldiimidazole (26 mg). The mixture was stirred at room temperature for 2 h, then a 0.5M solution of NH_3 in 1,4-dioxane (5 mL) was added and stirring at room temperature was continued for 2 h. Concentration and purification by chromatography (silica, CH_2Cl_2/MeOH) afforded the title compound as a colorless solid (29 mg, 60%). $[MH]^+ = 468$.

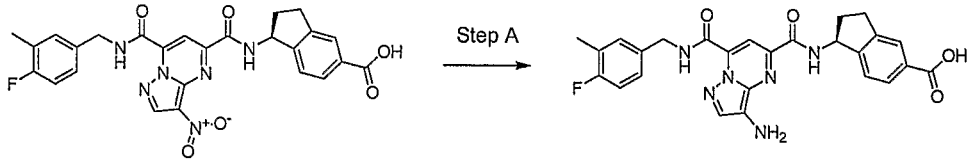
Example 466



[0577] Step A

The title compound from the Example 361 (45 mg) was treated similarly as described in the Example 465, Step A to afford the title compound (21 mg, 48%). $[MH]^+ = 468$.

Example 467

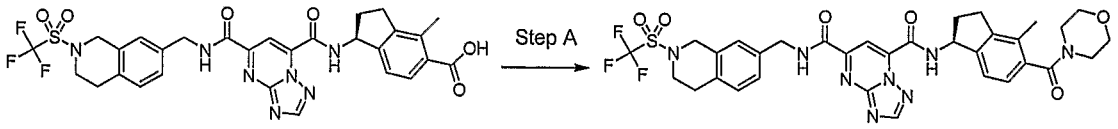


[0578] Step A

A mixture of the title compound from the Example 321 (10 mg) and Pd/C (10wt%, 5 mg) in EtOH was hydrogenated at atmospheric pressure for 5 h, filtered, concentrated and

purified by preparative thin layer chromatography (silica, $CHCl_3$/MeOH) to afford the title compound (1 mg, 10%). $[MH]^+ = 503$.

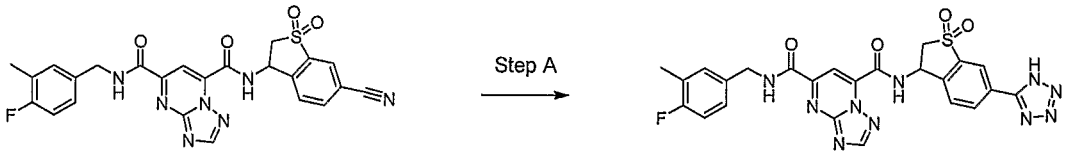
Example 468



[0579] Step A

To a solution of the title compound from the Example 381 (26 mg) in DMF (3 mL) was added morpholine (80 μL), EDCI (10 mg) and HOAt (5 mg). The mixture was stirred overnight and then concentrated. The remaining residue was dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$, 1N aqueous HCl and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to afford the title compound as a colorless solid (9.9 mg, 34%). $[MH]^+ = 727$.

Example 469



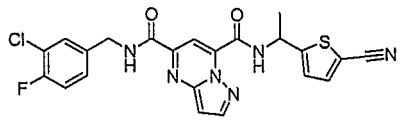
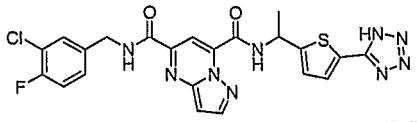
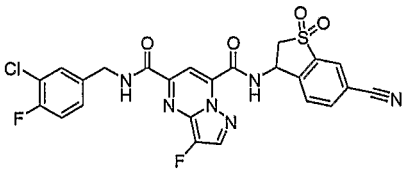
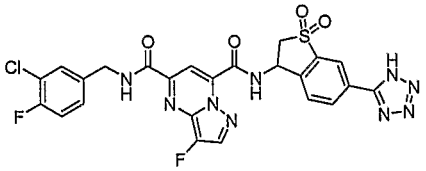
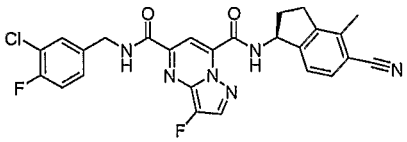
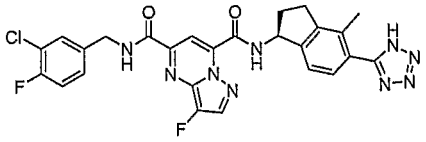
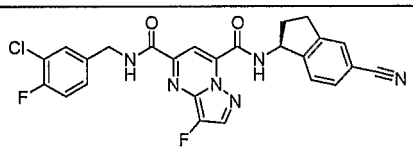
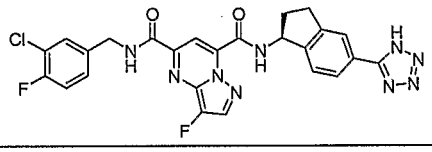
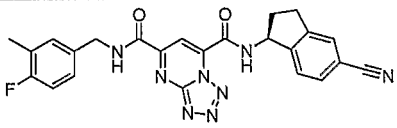
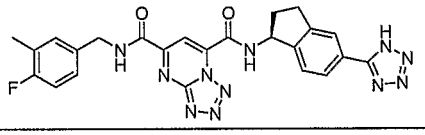
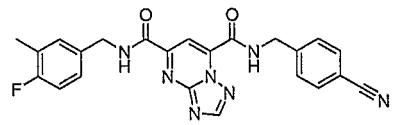
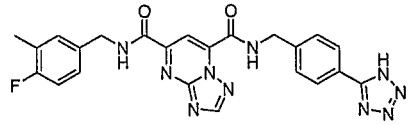
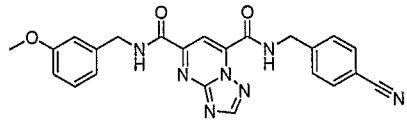
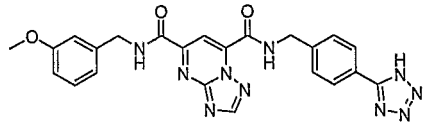
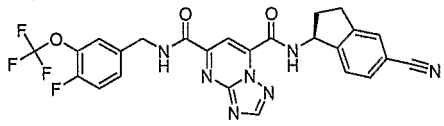
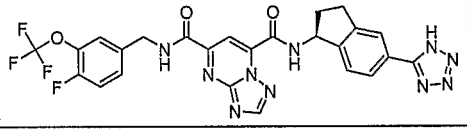
[0580] Step A

In a sealed vial was a mixture of the title compound from the Example 3, Step A (54 mg), dibutyltin oxide (15 mg) and azidotrimethylsilane (400 μL) in toluene (10 mL) under an argon atmosphere heated at 110°C for 18 h. The reaction mixture was then diluted with MeOH, concentrated and purified by chromatography (silica, CH_2Cl_2/MeOH) to give the title compound as an off-white solid (8.6 mg, 15%). $[MH]^+ = 563$.

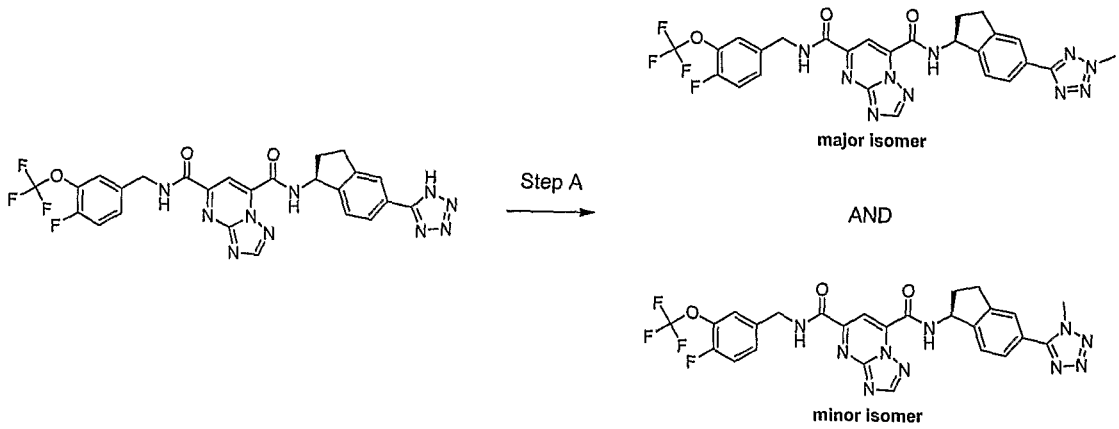
Examples 470-477

[0581] Following a similar procedure as described in the Example 469, except using the nitriles indicated in Table II-8 below, the following compounds were prepared.

Table II-8

Ex. #	nitrile	product	yield
470			74% $[MH]^+ = 526$
471			34% $[MH]^+ = 600$
472			38% $[MH]^+ = 564$
473			40% $[MH]^+ = 550$
474			55% $[MH]^+ = 514$
475			27% $[MH]^+ = 487$
476			46% $[MH]^+ = 485$
477			53% $[MH]^+ = 583$

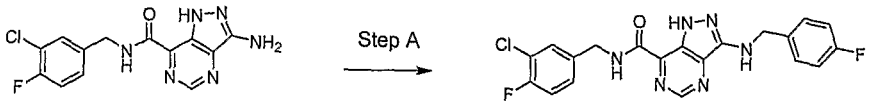
Example 478



[0582] Step A

To a solution of the title compound from the Example 477 (80 mg) in DMF (3 mL) were added iodomethane (9 μL) and K_2CO_3 (19 mg) and the mixture was stirred at room temperature overnight. Additional iodomethane (8 μL) was added and stirring at room temperature was continued for 2 h. The mixture was concentrated and purified by preparative thin layer chromatography (silica, EtOAc) to afford the major isomer (30 mg, 37%) and the minor isomer (15 mg, 18%) of the title compound. $[MH]^+ = 597$.

Example 479



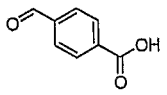
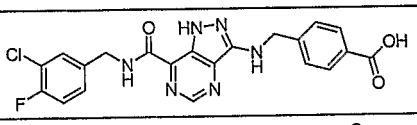
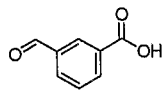
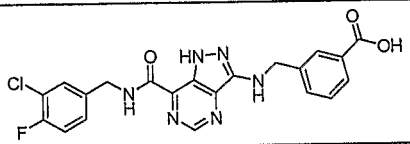
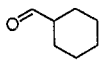
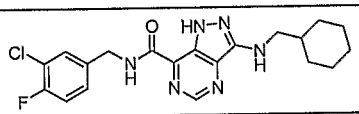
[0583] Step A

To a stirring solution of the title compound from the Preparative Example 377, Step E (9 mg) in MeOH (3 mL) were added AcOH (a few drops), a 1M solution of commercially available 4-fluorobenzaldehyde in MeOH (30 μL) and $NaBH(OAc)_3$ (5 mg). The mixture was stirred at room temperature overnight, concentrated, diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), filtered, concentrated and purified by preparative thin layer chromatography (silica, cyclohexane/EtOAc) to afford the title compound as an off-white solid (5 mg, 42%). $[MH]^+ = 429$.

Example 480-482

[0584] Following similar procedures as described in the Example 479, except using the aldehydes indicated in Table II-9 below, the following compounds were prepared.

Table II-9

Ex. #	aldehyde	product	yield
480			>99% $[MH]^+ = 455$
481			63% $[MH]^+ = 455$
482			n.d. $[MH]^+ = 417$

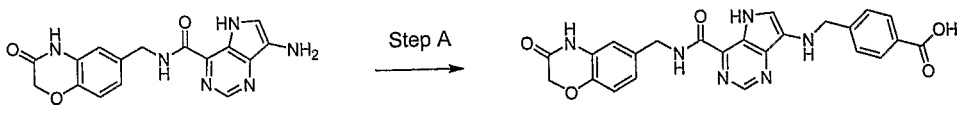
Example 483



[0585] Step A

To a solution of the title compound from the Preparative Example 379, Step G (7 mg) in anhydrous pyridine (1 mL) was added Ac_2O (1 mL). The mixture was stirred at room temperature for 5 h, concentrated and slurried in MeOH. The formed precipitate was collected by filtration and dried to afford the title compound as a brown solid (5.1 mg, 64%). $[MH]^+ = 381$.

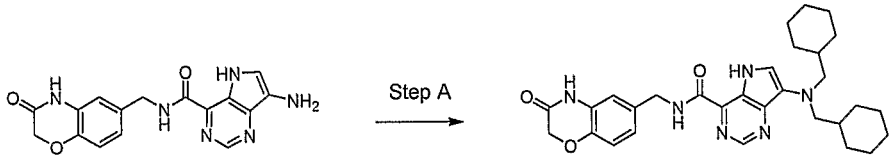
Example 484



[0586] Step A

A stirring solution of the title compound from the Preparative Example 377, Step G (9 mg) in MeOH/H_2O/THF (3:2:1, 6 mL) was adjusted to pH 6 with 3M aqueous NaOAc. 4-Formylbenzoic acid (6 mg) was added and the mixture was stirred at room temperature for 30 min. $NaBH_3CN$ (5 mg) was added and stirring at room temperature was continued overnight. The mixture was concentrated and diluted with 0.1N aqueous HCl (5 mL). The formed precipitate was collected by filtration, washed with 0.1N aqueous HCl (8 mL) and dried to afford the title compound as an orange solid (7.8 mg, 61%). $[MH]^+ = 473$.

Example 485



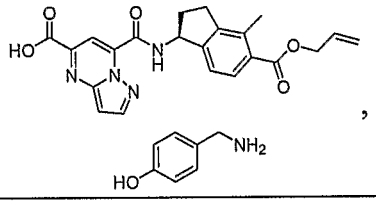
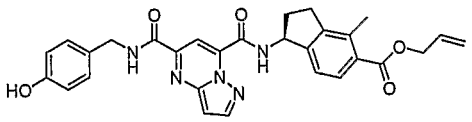
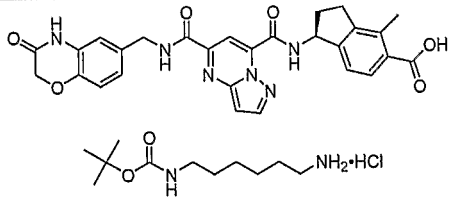
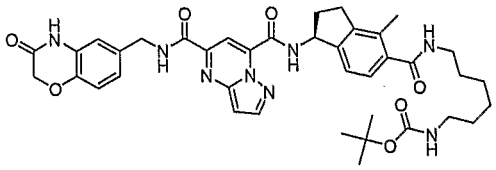
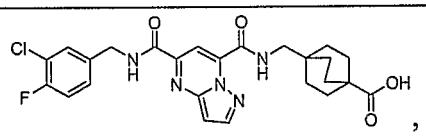
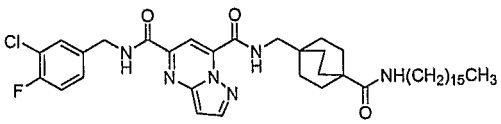
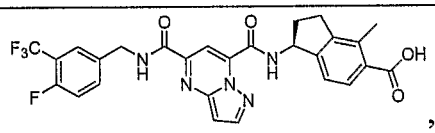
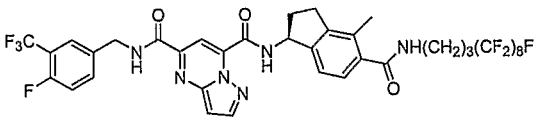
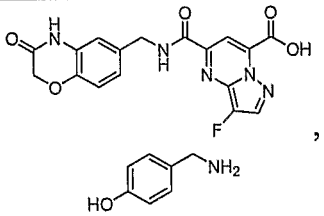
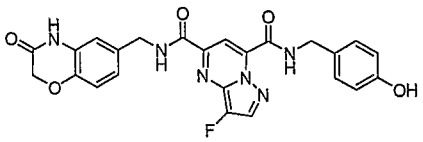
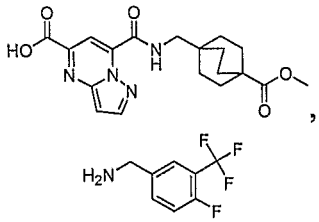
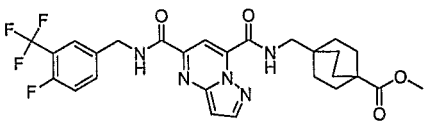
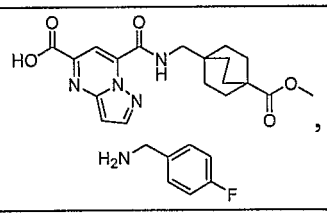
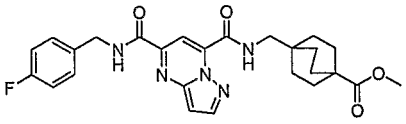
[0587] Step A

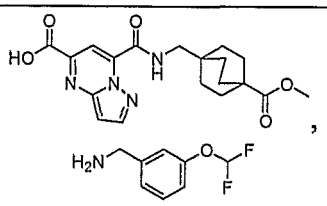
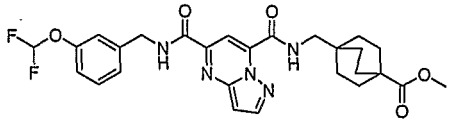
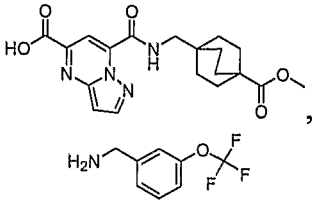
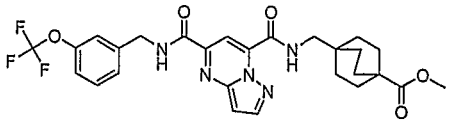
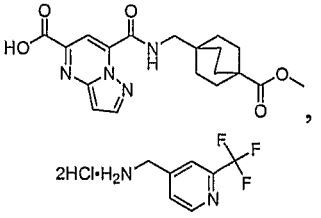
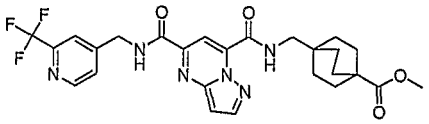
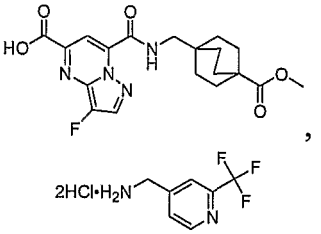
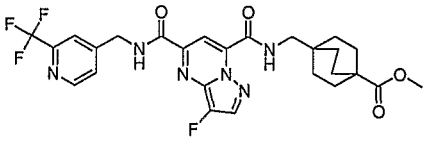
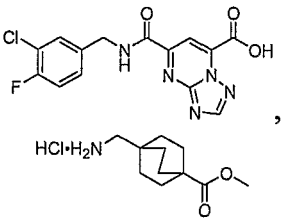
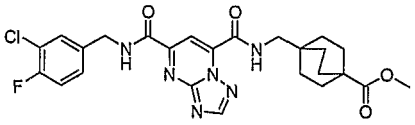
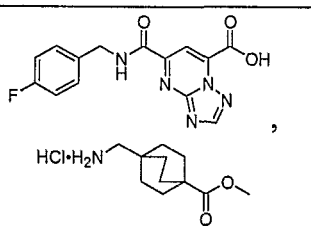
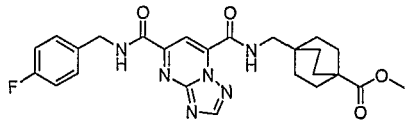
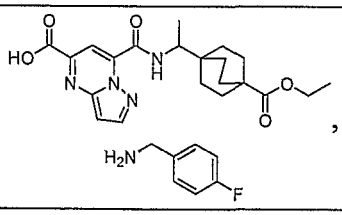
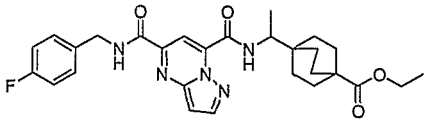
The title compound from the Preparative Example 377, Step G (9 mg) was treated similarly as described in the Preparative Example 484, except using cyclohexanecarbaldehyde (0.04 mL) instead of 4-formylbenzoic acid to afford the title compound as a reddish glass (6.5 mg, 45%). $[MH]^+ = 531$.

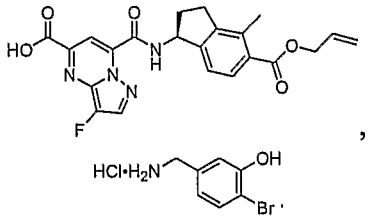
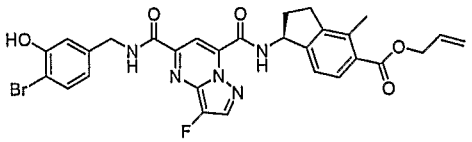
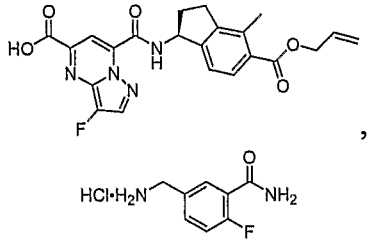
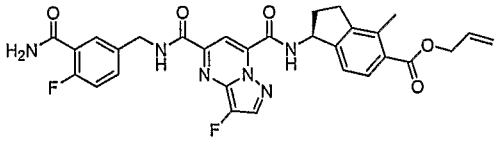
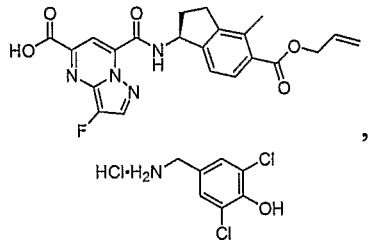
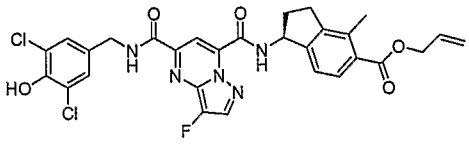
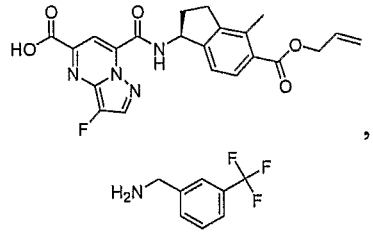
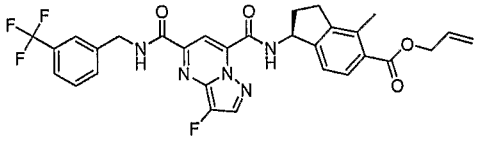
Examples 486-504

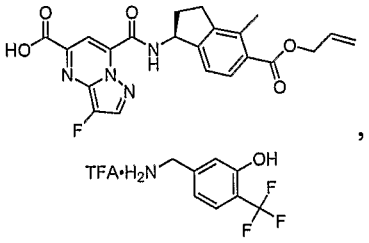
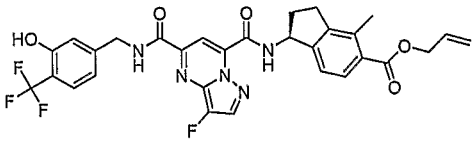
[0588] Following similar procedures as described in the Examples 1 (method A), 2 (method B), 3 (method C), 4 (method D), 5 (method E), 6 (method F) or 7 (method G), except using the acids and amines indicated in Table II-10 below, the following compounds were prepared.

Table II-10

Ex. #	acid, amine	product	method, yield
486			B, n.d. $[MH]^+ = 526$
487			B, 34% $[MH]^+ = 739$
488	 $H_2N(CH_2)_{15}CH_3$		B, 75% $[MH]^+ = 738$
489	 $H_2N(CH_2)_3(CF_2)_8F$		B, n.d. $[MH]^+ = 1015$
490			B, 31% $[MH]^+ = 491$
491			C, 77% $[MH]^+ = 562$
492			C, 69% $[MH]^+ = 494$

Ex. #	acid, amine	product	method, yield
493			C, 71% $[MH]^+ = 542$
494			C, 69% $[MH]^+ = 560$
495			C, 54% $[MH]^+ = 545$
496			C, 55% $[MH]^+ = 563$
497			C, 90% $[MH]^+ = 529$
498			C, 90% $[MH]^+ = 495$
499			C, n.d. $[MH]^+ = 522$

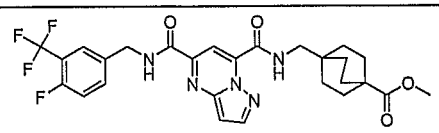
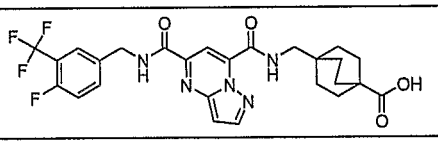
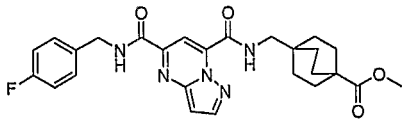
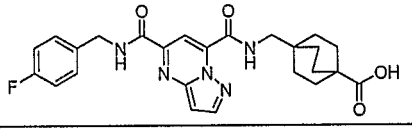
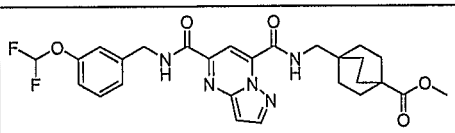
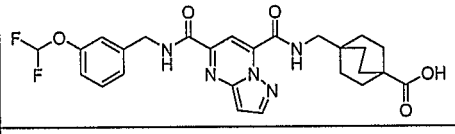
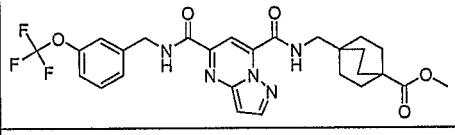
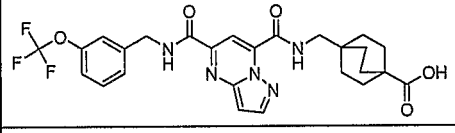
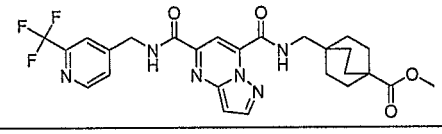
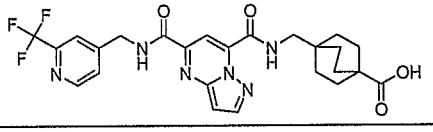
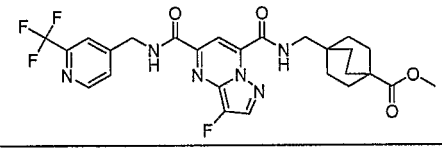
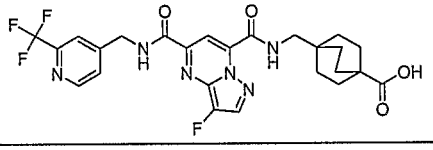
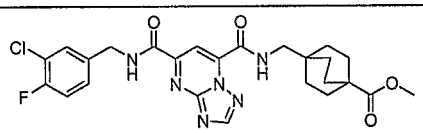
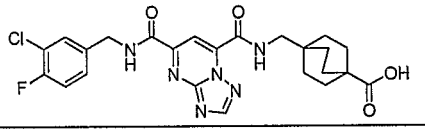
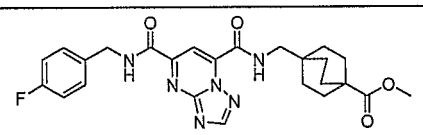
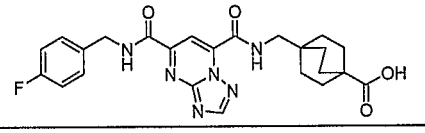
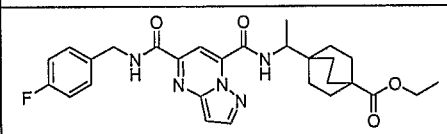
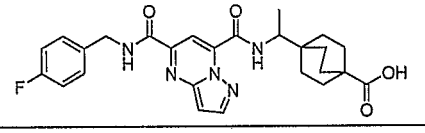
Ex. #	acid, amine	product	method, yield
500			C, 33% $[M-"indene"]^+ = 408$
501			C, n.d. $[MH]^+ = 571$
502			C, n.d. $[MH]^+ = 612$
503			C, 40% $[MNa]^+ = 618$

Ex. #	acid, amine	product	method, yield
504	 ,		C, 40% ^{1}H-NMR ($CDCl_3$) δ = 10.34 (d, 1 H), 8.69 (s, 1 H), 8.08 (t, 1 H), 8.06 (d, 1 H), 7.78 (d, 1 H), 7.47 (d, 1 H), 7.20-7.24 (m, 1 H), 6.95-7.02 (m, 2 H), 5.93-6.08 (m, 2 H), 5.72-5.82 (m, 1 H), 5.37 (dd, 1 H), 5.25 (dd, 1 H), 4.78 (d, 2 H), 4.67 (d, 2 H), 3.00-3.16 (m, 1 H), 2.71-2.95 (m, 2 H), 2.50 (s, 3 H), 1.96-2.10 (m, 1 H)

Examples 505-513

[0589] Following similar procedures as described in the Examples 314 (method A) or 315 (method B), except using the esters indicated in Table II-11 below, the following compounds were prepared.

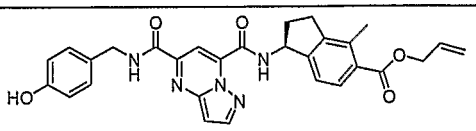
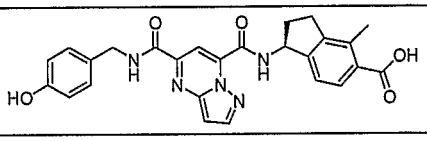
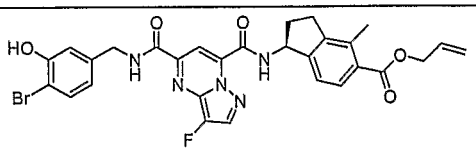
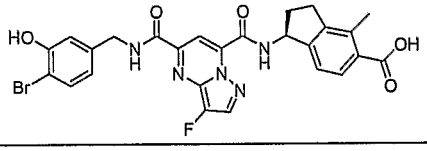
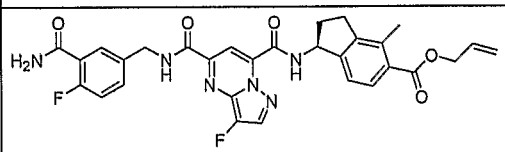
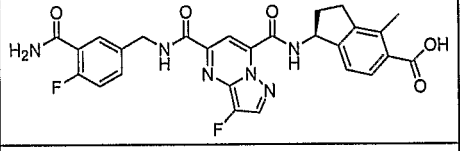
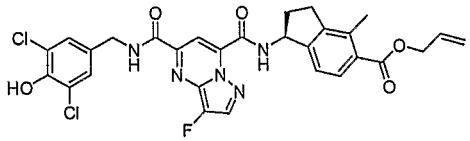
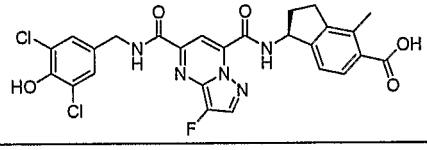
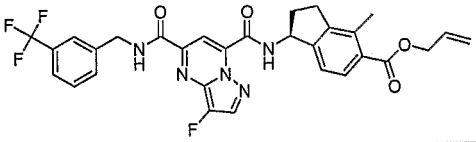
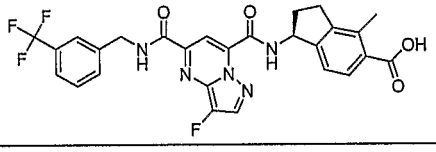
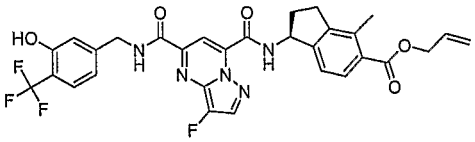
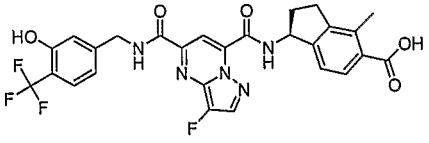
Table II-11

Ex. #	ester	product	method, yield
505			A, 41% $[MH]^+ = 548$
506			A, 49% $[MH]^+ = 480$
507			A, 39% $[MH]^+ = 528$
508			A, 49% $[MH]^+ = 546$
509			A, n.d. $[MH]^+ = 531$
510			A, n.d. $[MH]^+ = 549$
511			B, n.d. $[MH]^+ = 515$
512			B, n.d. $[MH]^+ = 481$
513			A, n.d. $[MH]^+ = 508$

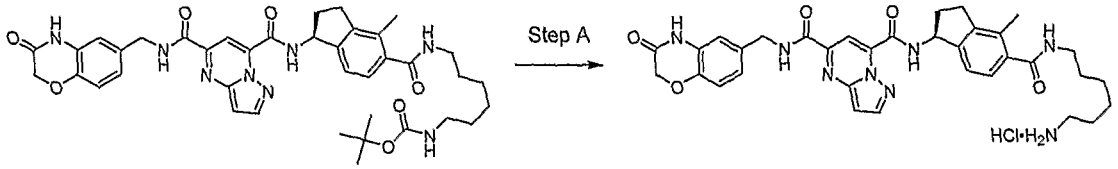
Examples 514-518

[0590] Following a similar procedure as described in the Example 362, except using the esters indicated in Table II-12 below, the following compounds were prepared.

Table II-12

Ex. #	ester	product	yield
514			n.d.% $[MH]^+ = 486$
515			17% $[M-"indene"]^+ = 408$
516			n.d. $[MH]^+ = 549$
517			n.d. $[MH]^+ = 572$
517			>99% $[MH]^+ = 556$
518			69% ^{1}H-NMR ($CDCl_3$) δ = 12.20-13.20 (br s, 1 H), 10.40-10.70 (br s, 1 H), 10.06 (d, 1 H), 9.73 (t, 1 H), 8.68 (d, 1 H), 8.07 (s, 1 H), 7.72 (d, 1 H), 7.49 (d, 1 H), 7.32 (d, 1 H), 7.04 (s, 1 H), 6.93 (d, 1 H), 5.61-5.71 (m, 1 H), 4.52 (d, 2 H), 2.80-3.11 (m, 2 H), 2.61-2.72 (m, 1 H), 2.50 (s, 3 H), 1.96-2.10 (m, 1 H)

Example 519



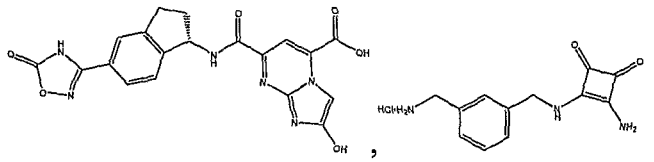
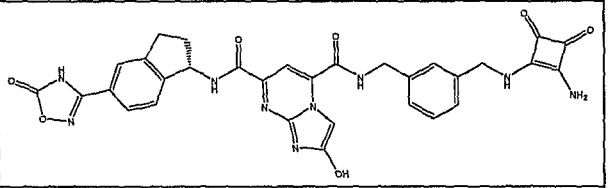
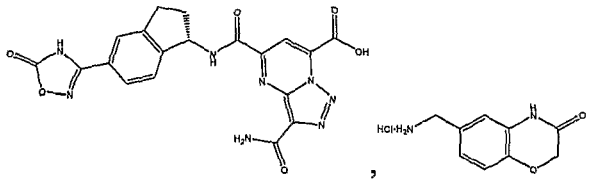
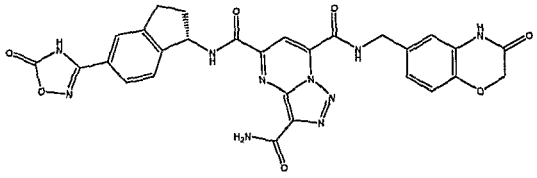
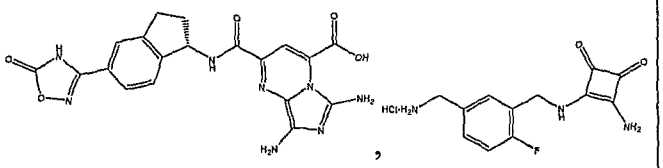
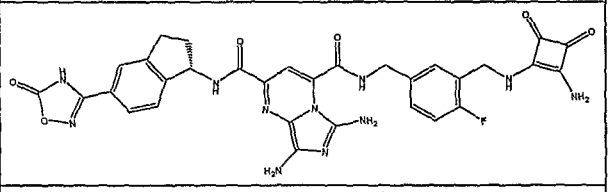
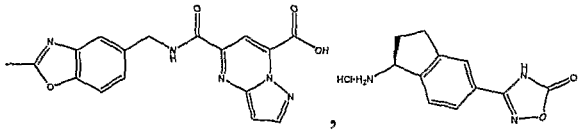
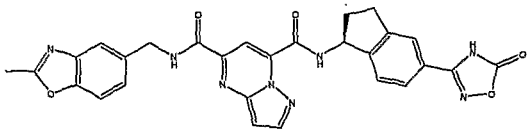
[0591] Step A

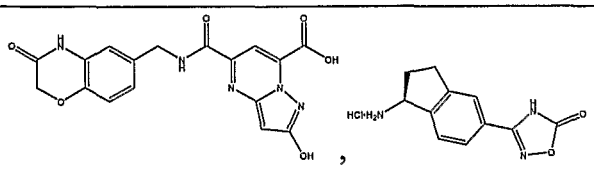
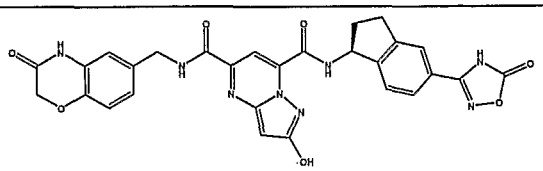
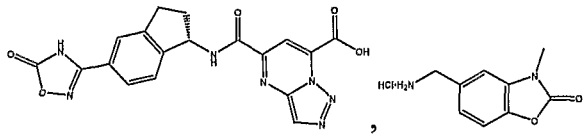
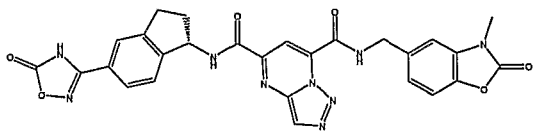
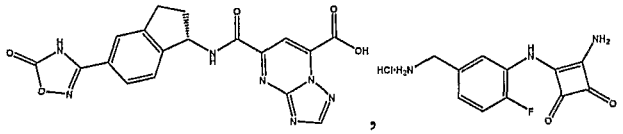
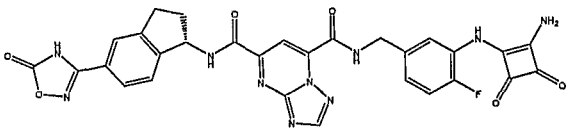
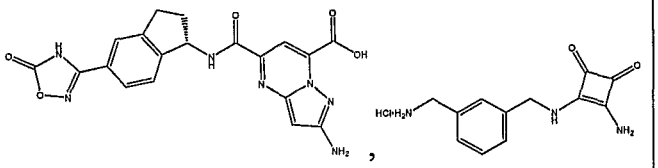
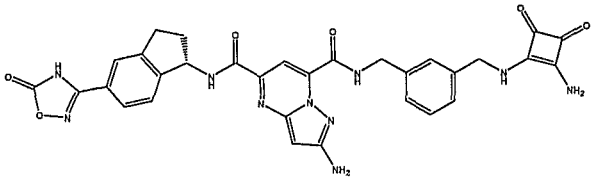
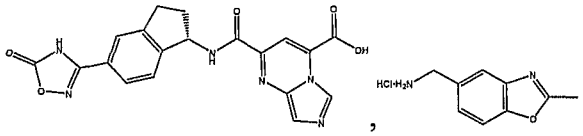
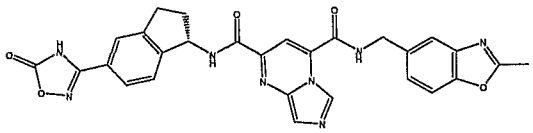
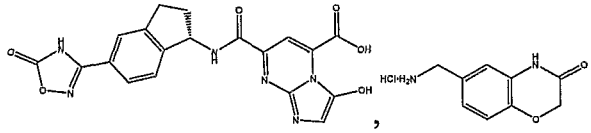
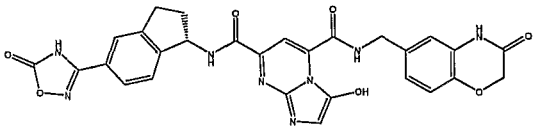
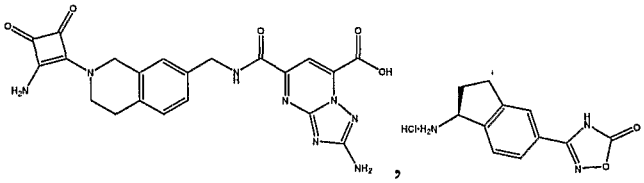
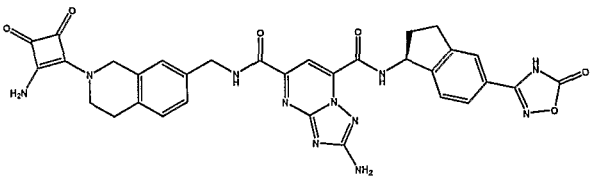
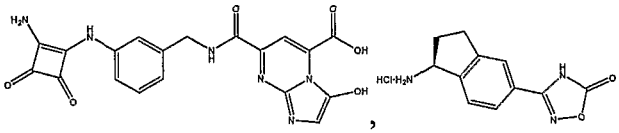
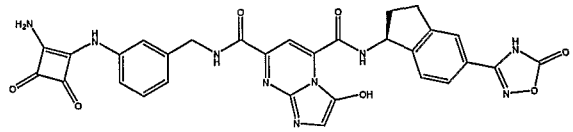
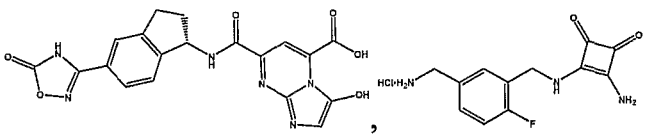
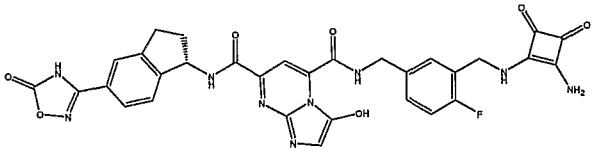
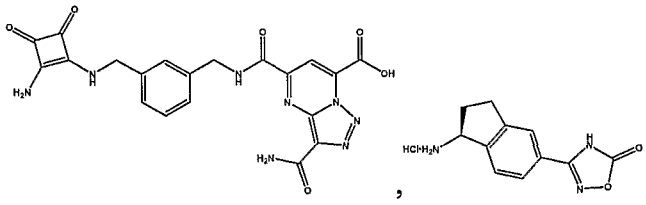
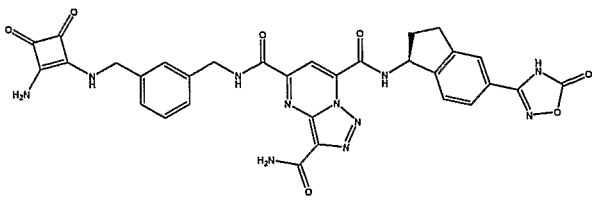
The title compound from the Example 487 (42 mg) was treated similarly as described in the Example 296, Step B to afford the title compound (44 mg, >99%). $[M-Cl]^+ = 639$.

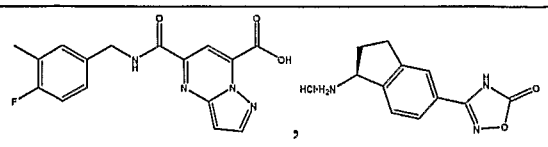
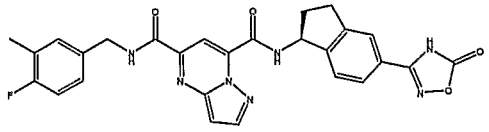
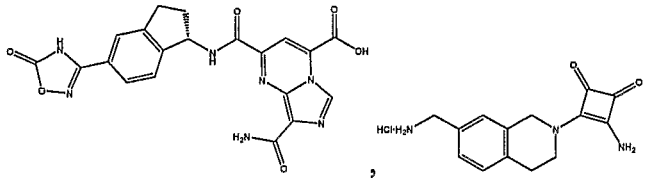
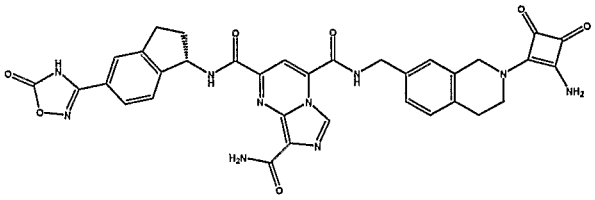
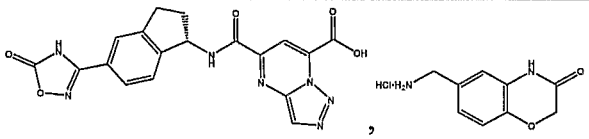
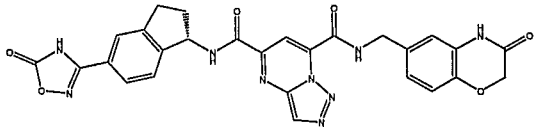
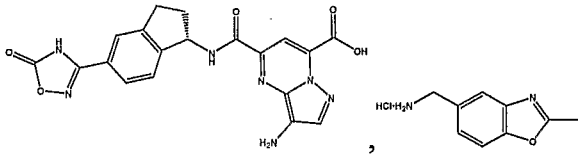
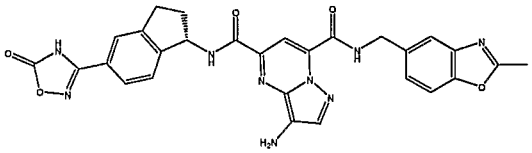
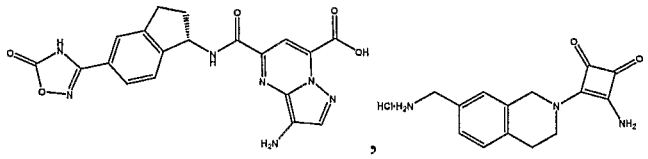
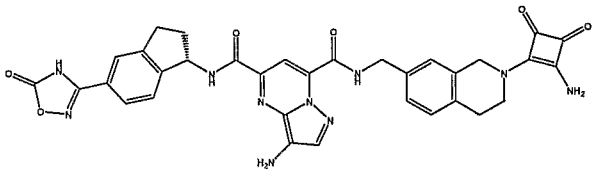
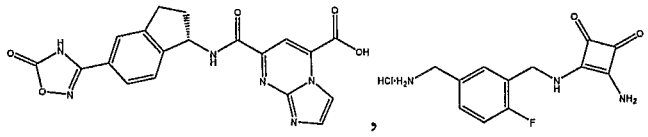
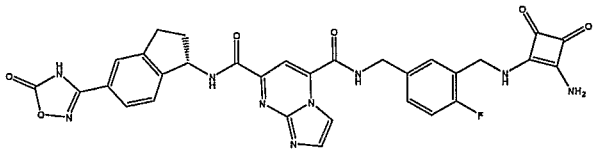
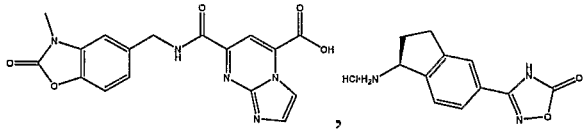
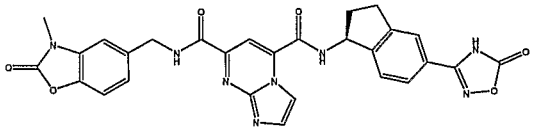
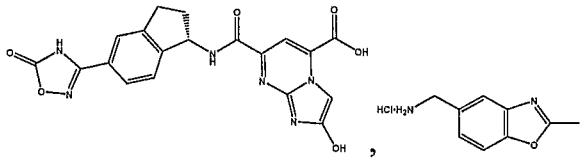
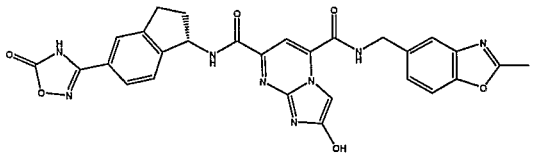
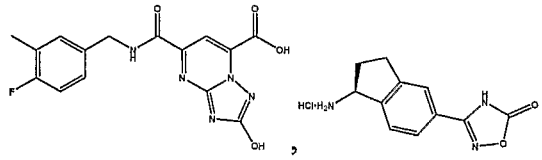
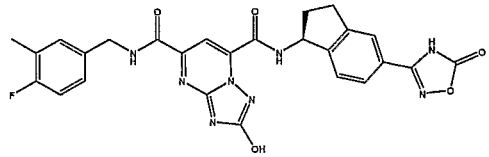
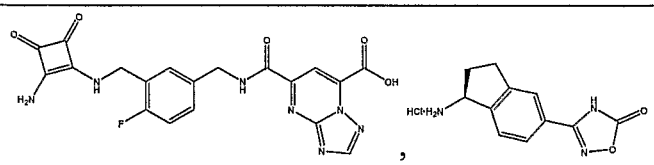
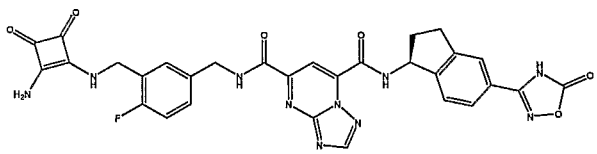
Examples 520-609

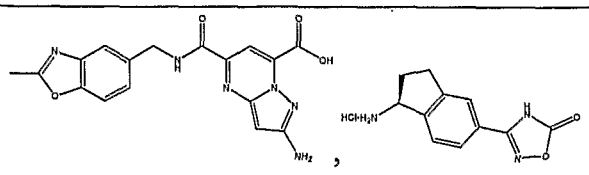
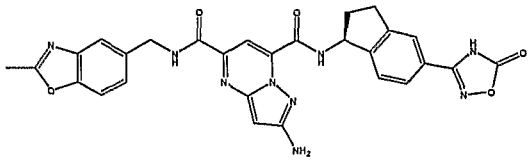
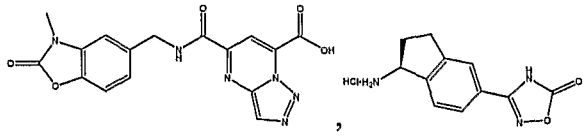
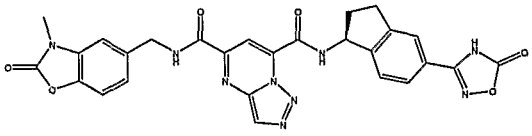
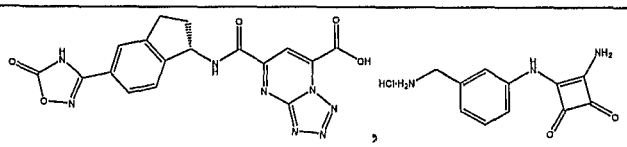
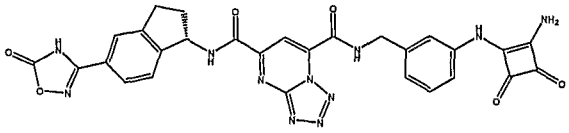
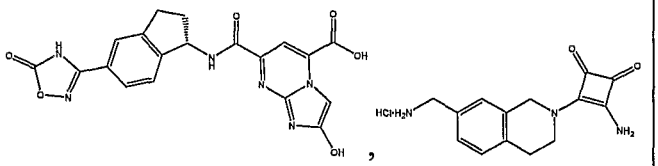
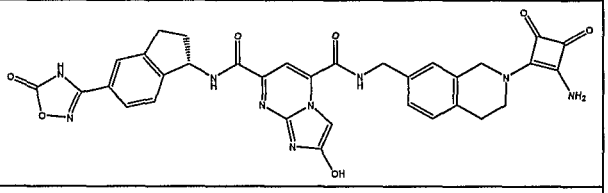
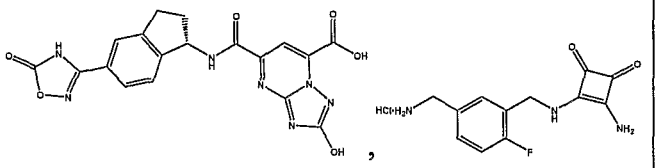
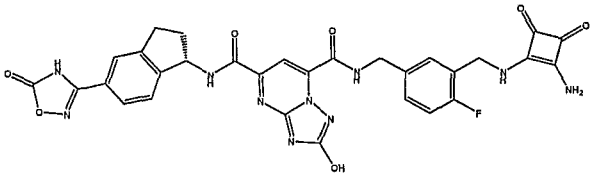
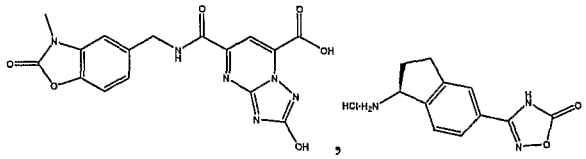
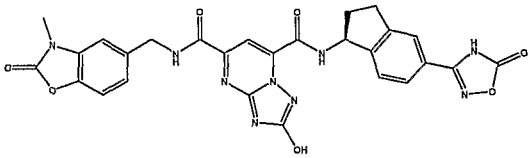
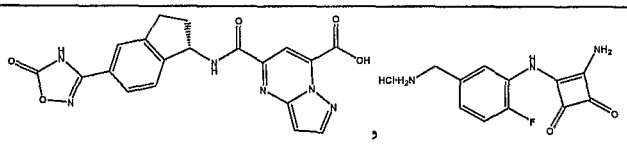
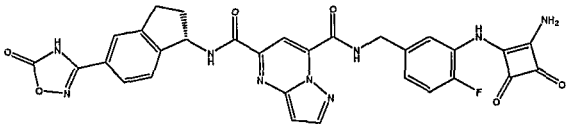
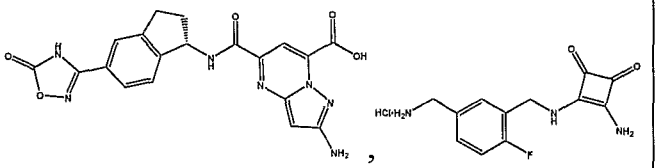
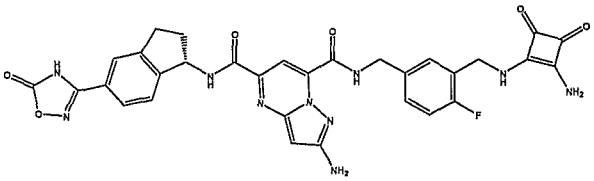
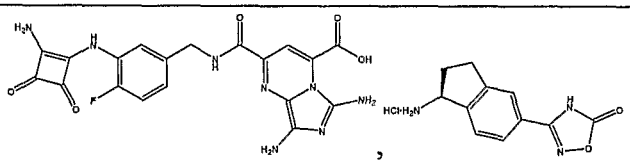
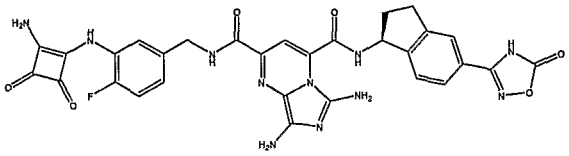
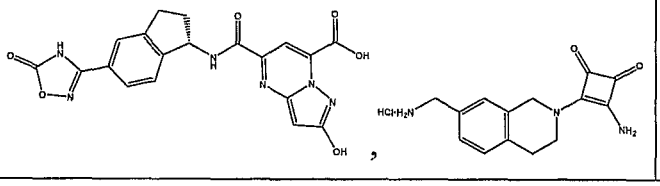
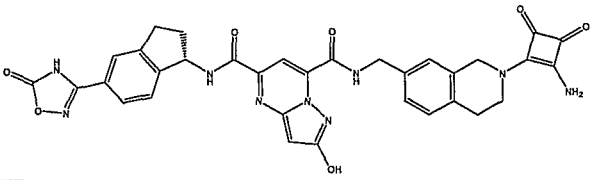
[0592] If one were to follow similar procedures as described in the Examples 1, 2, 3, 4, 5, 6 or 7, except using the acids and amines indicated in Table II-13 below, the following compounds would be obtained.

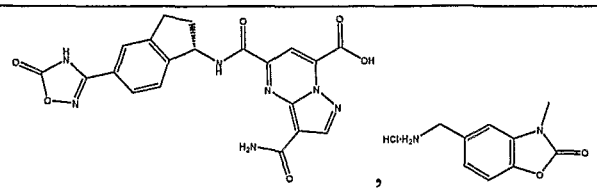
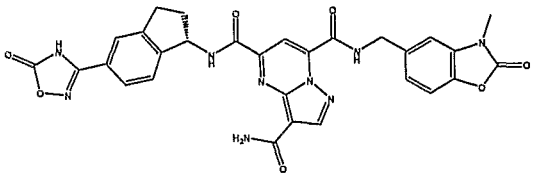
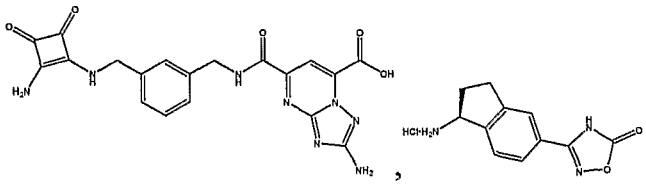
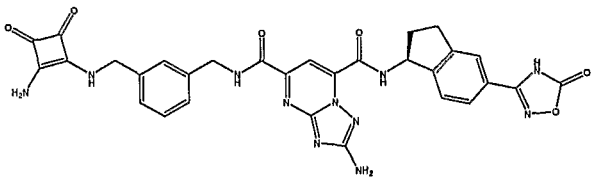
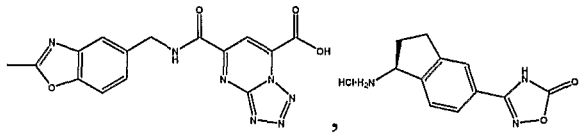
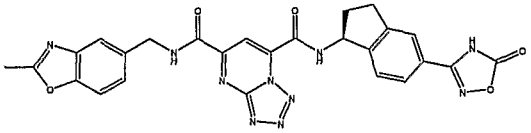
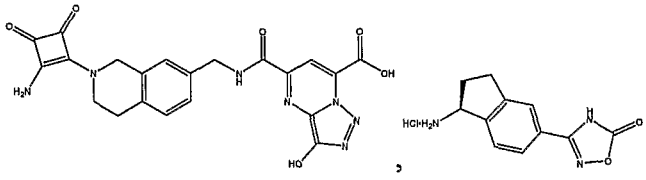
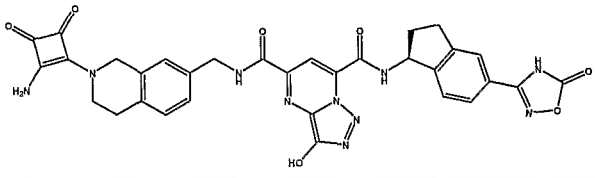
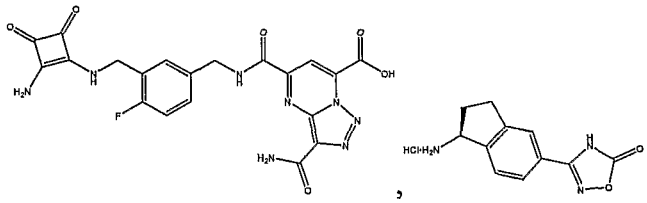
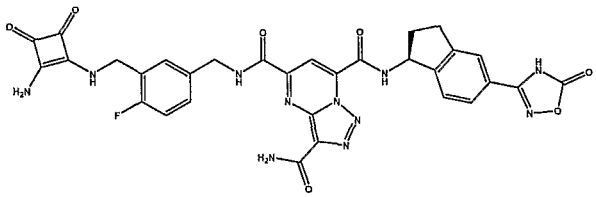
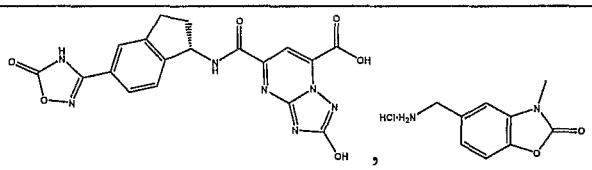
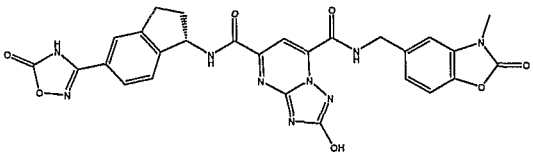
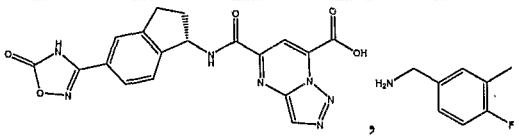
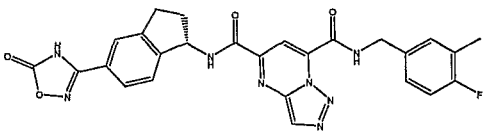
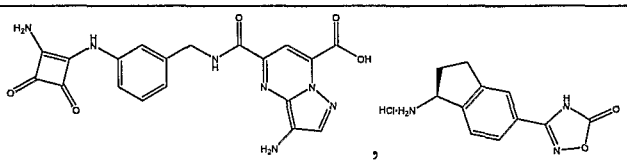
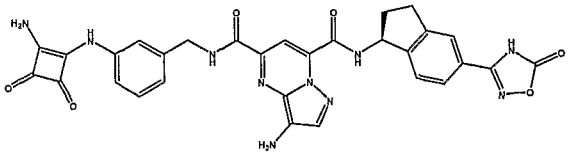
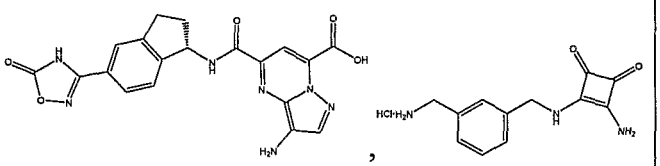
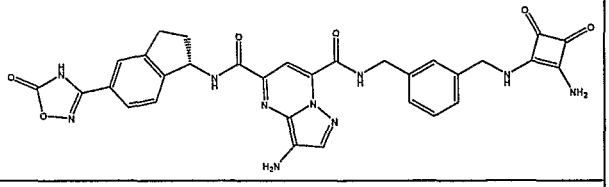
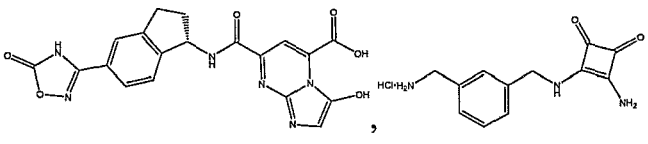
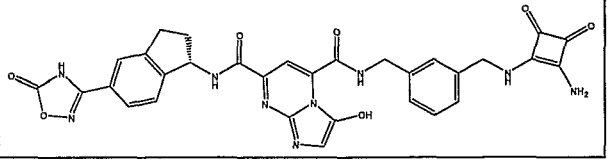
Table II-13

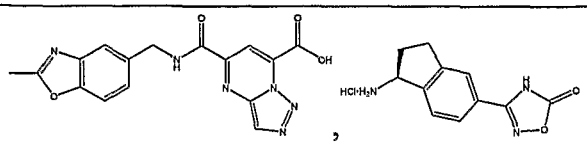
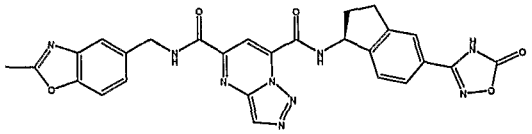
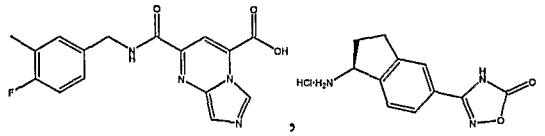
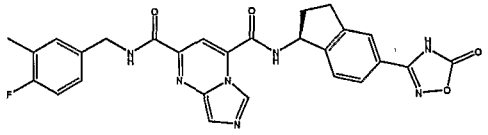
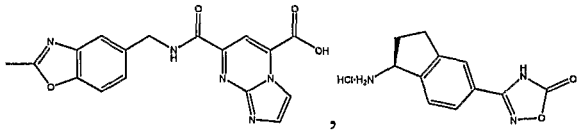
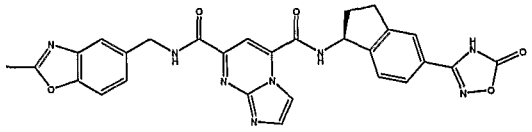
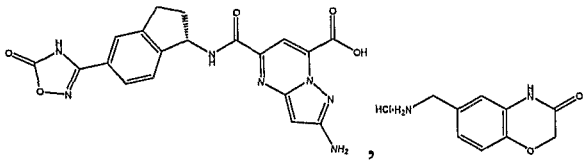
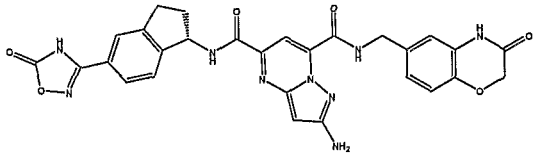
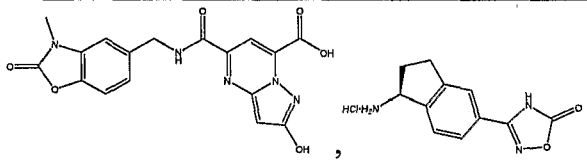
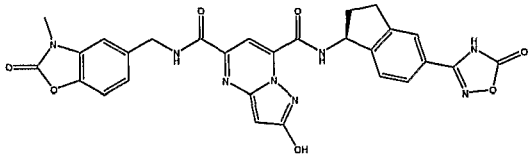
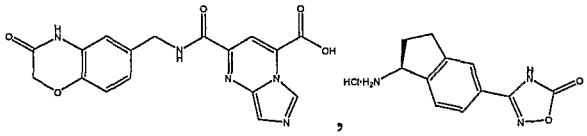
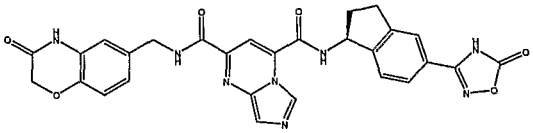
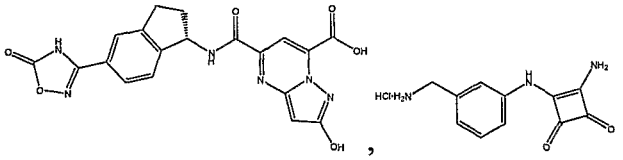
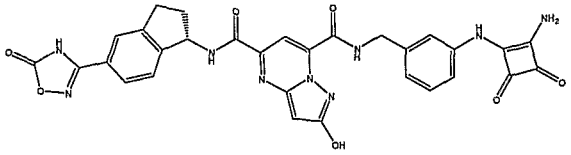
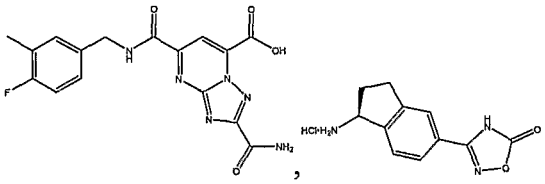
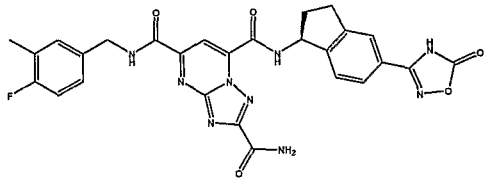
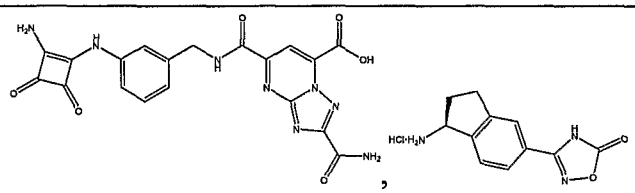
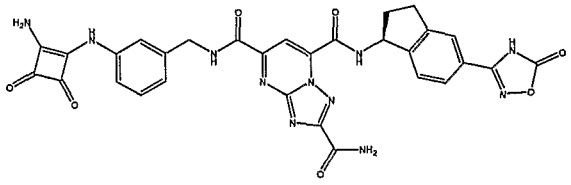
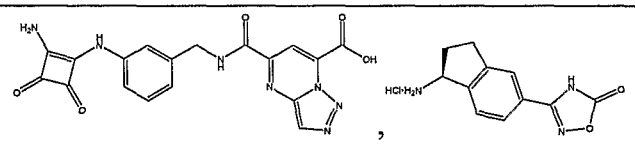
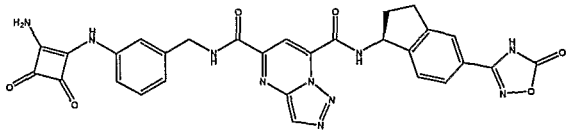
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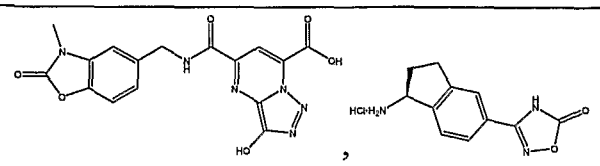
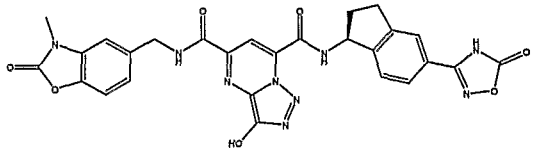
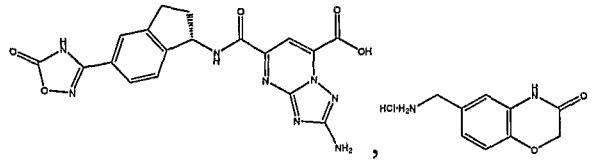
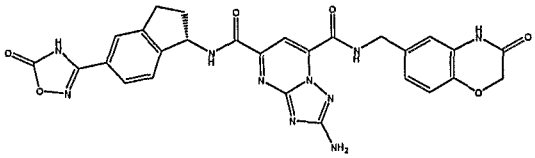
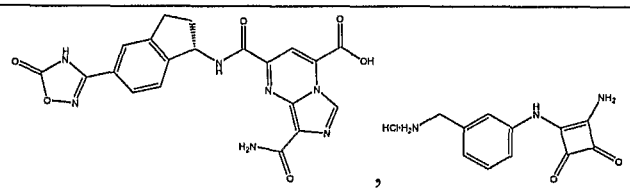
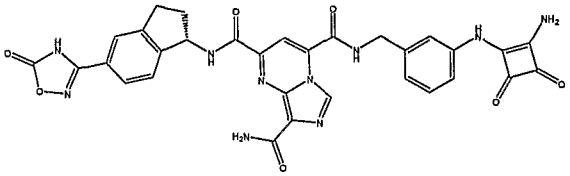
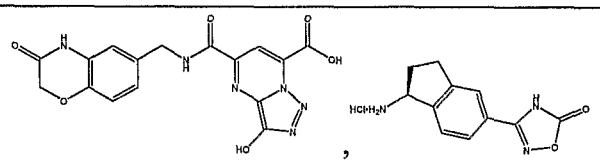
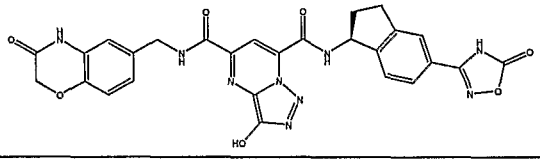
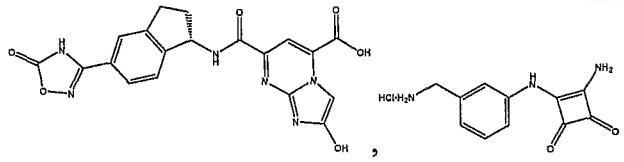
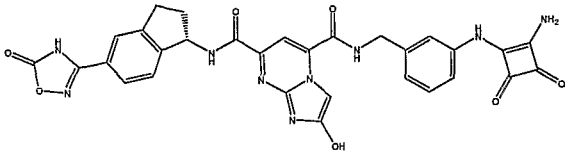
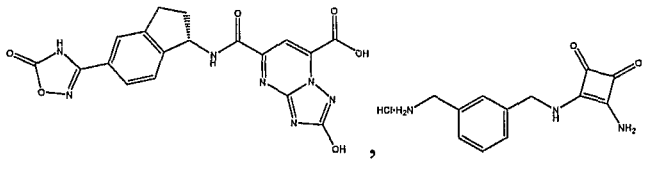
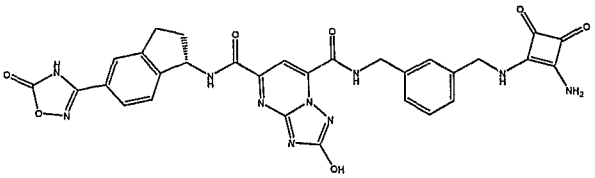
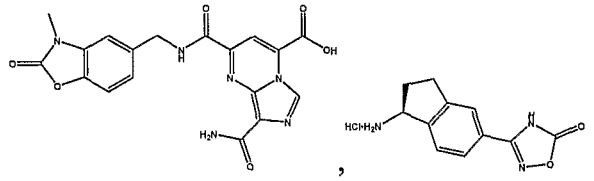
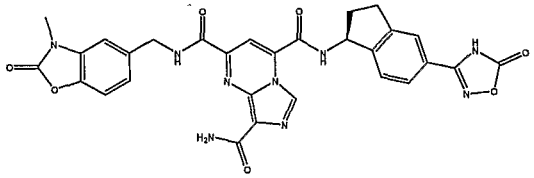
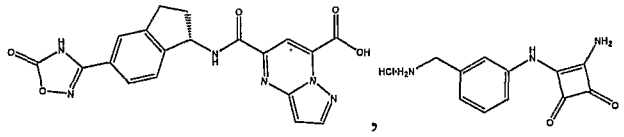
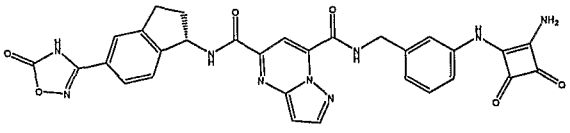
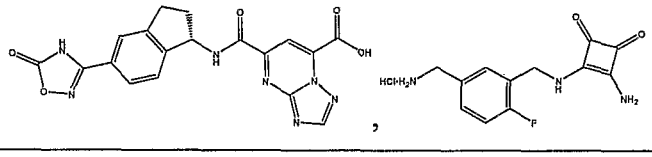
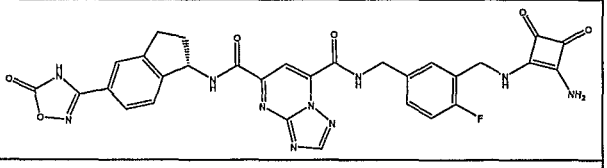
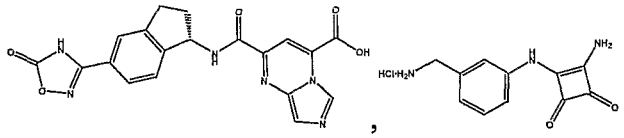
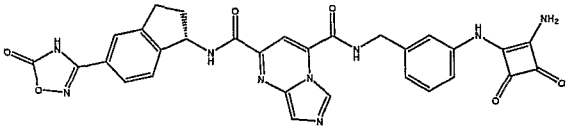
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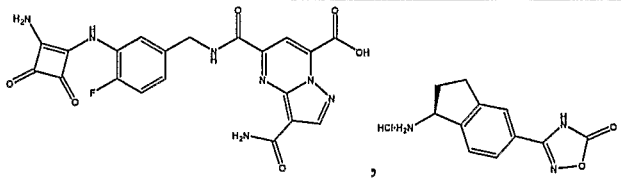
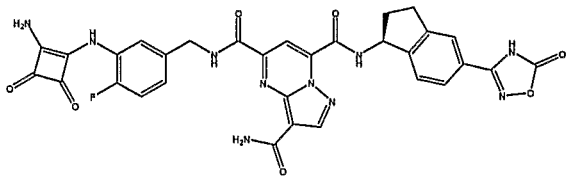
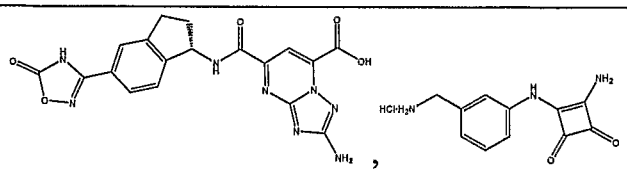
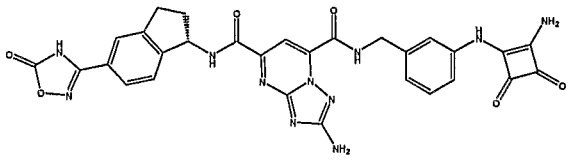
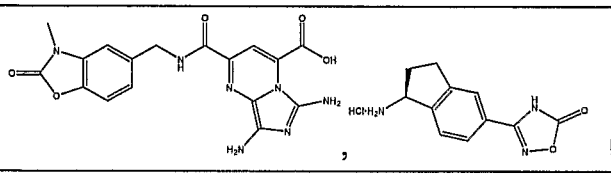
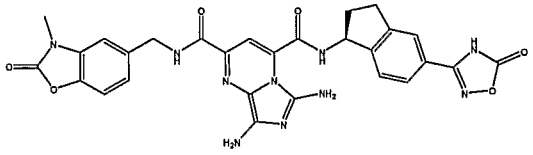
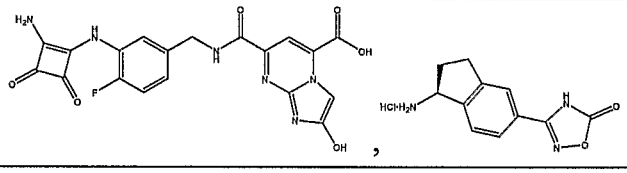
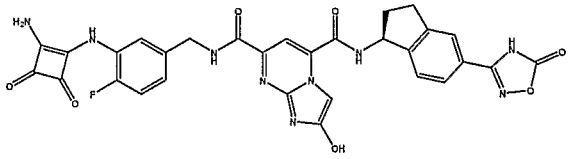
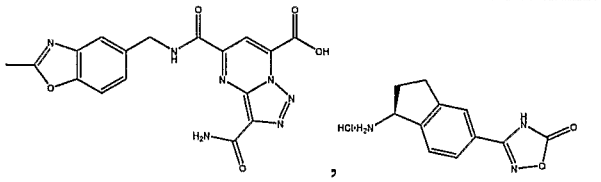
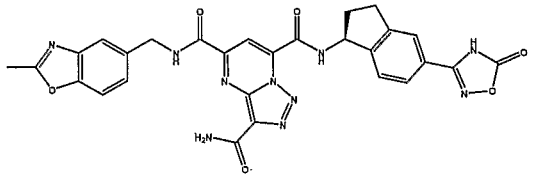
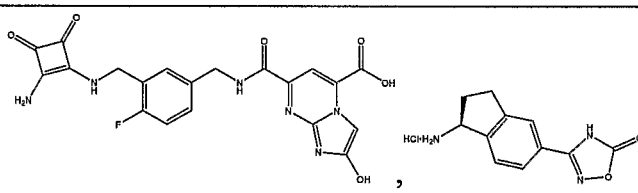
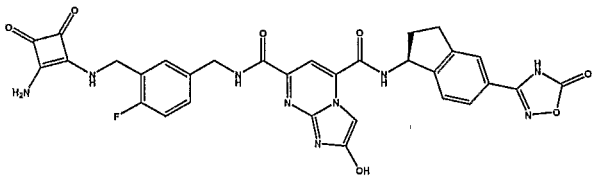
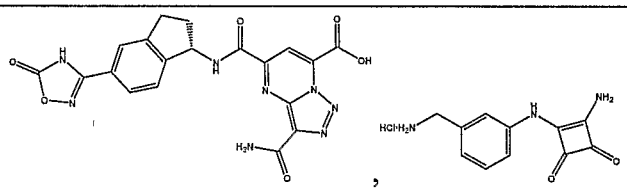
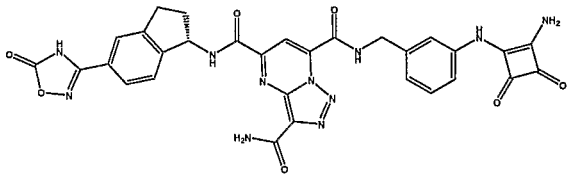
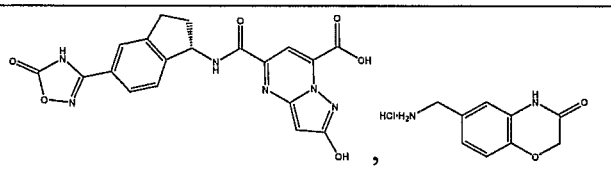
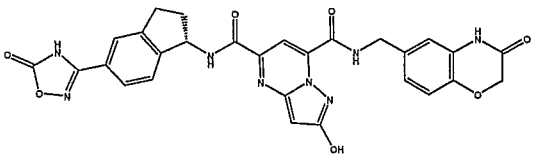
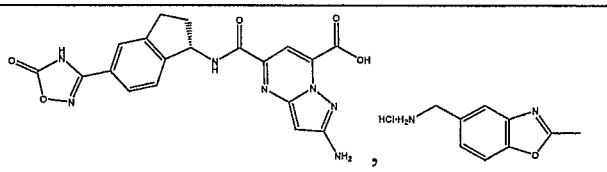
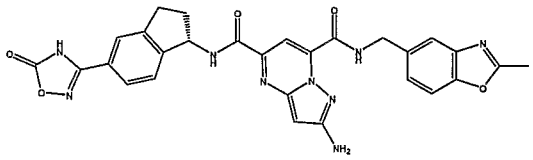
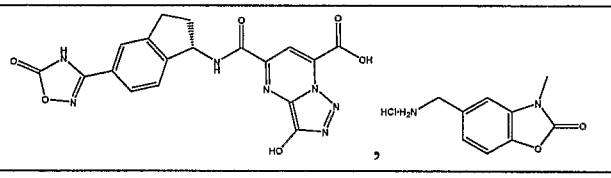
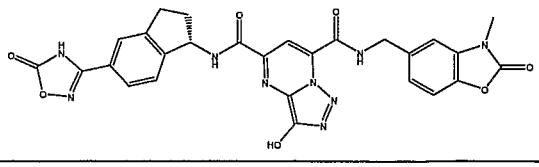
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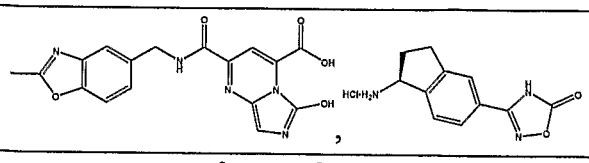
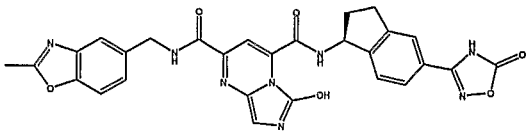
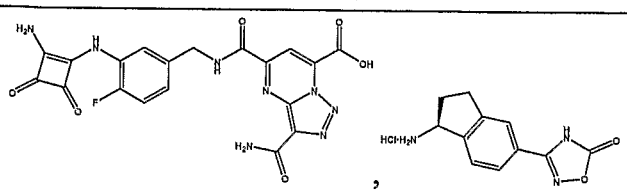
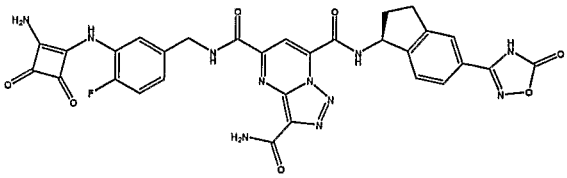
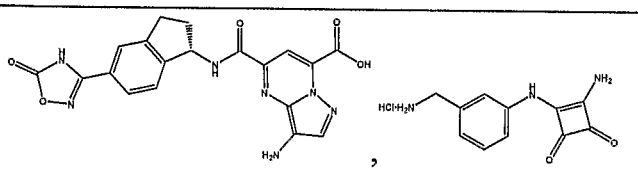
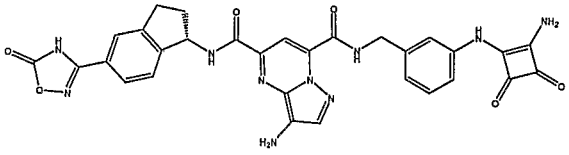
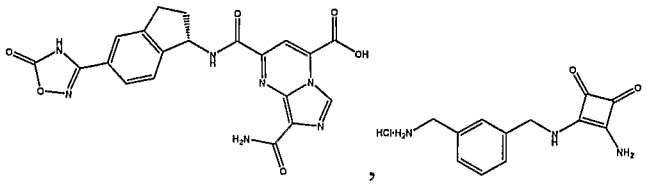
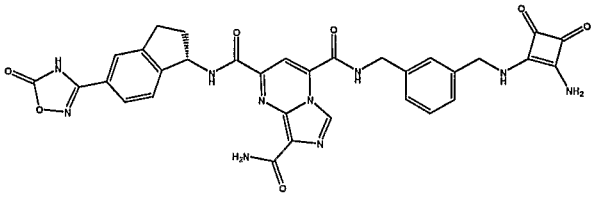
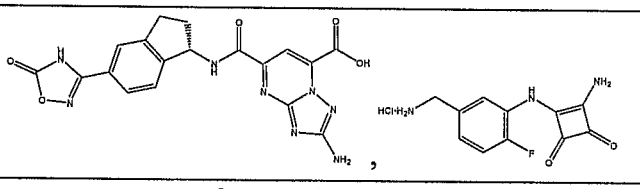
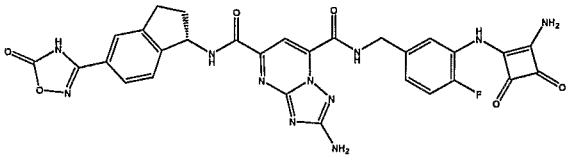
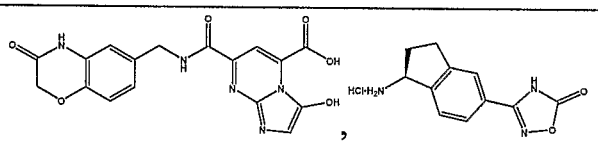
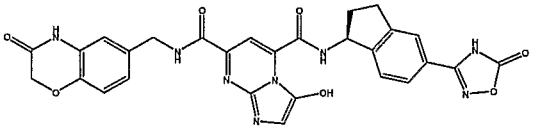
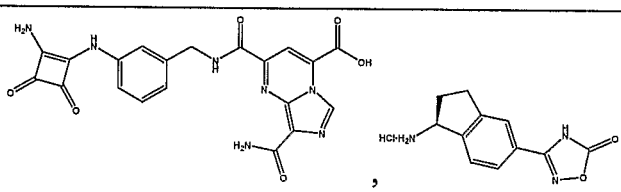
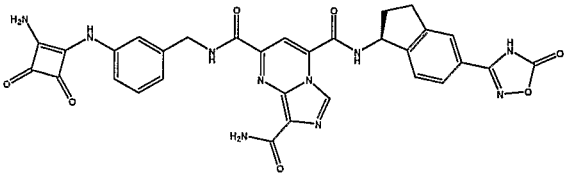
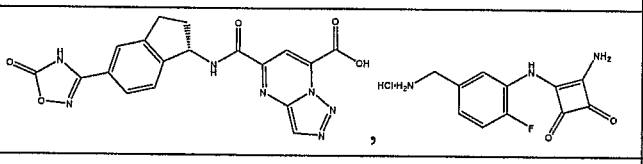
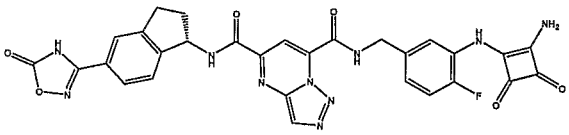
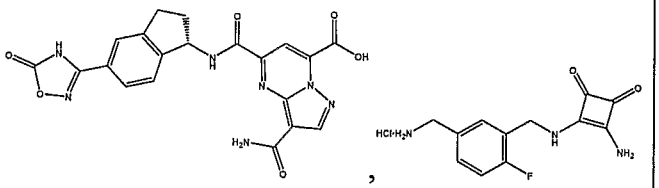
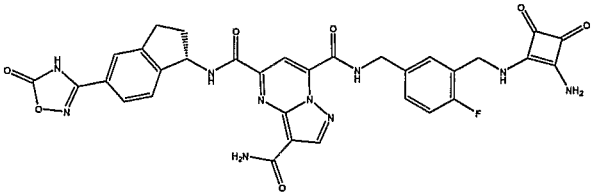
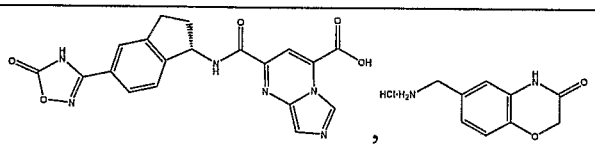
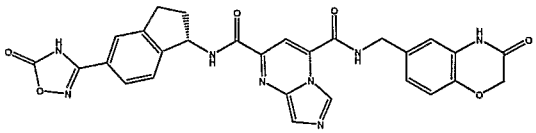
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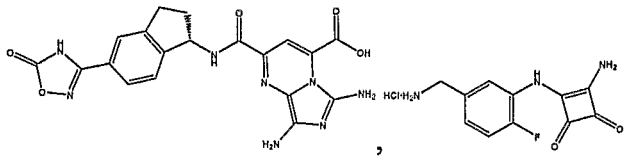
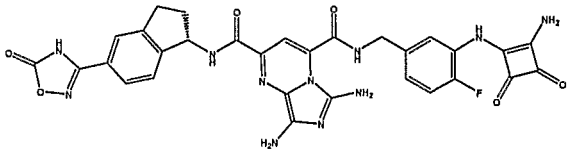
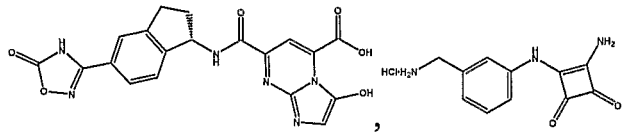
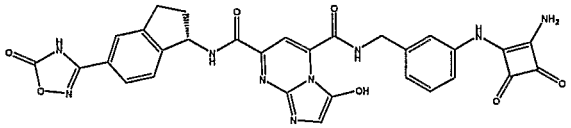
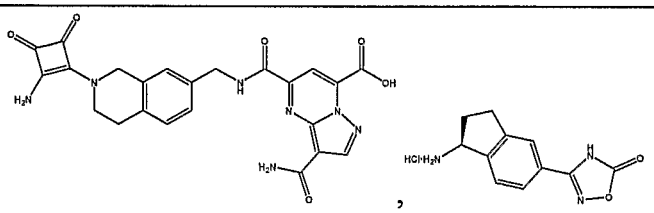
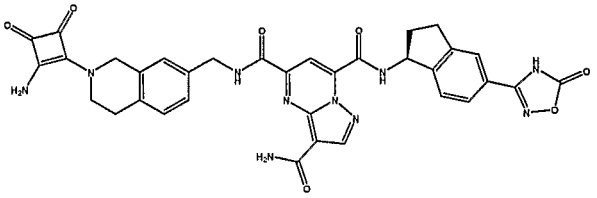
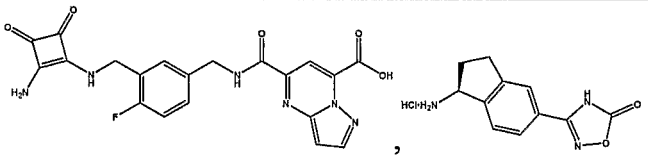
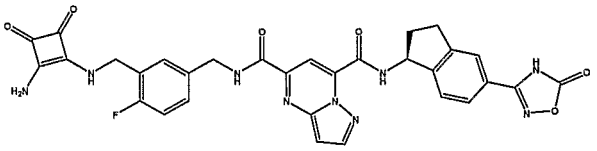
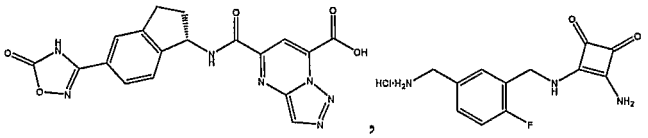
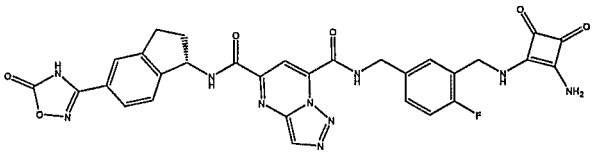
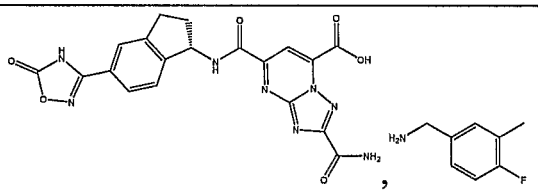
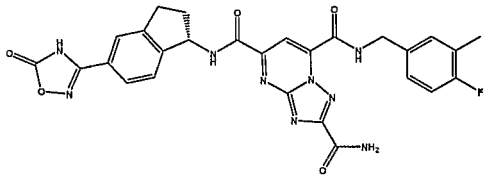
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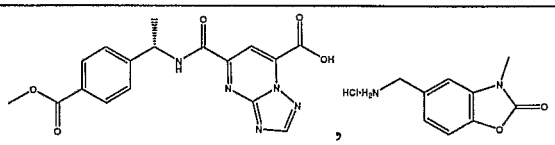
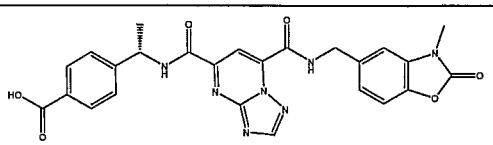
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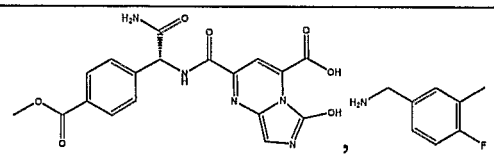
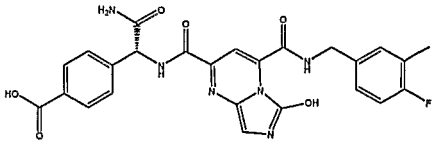
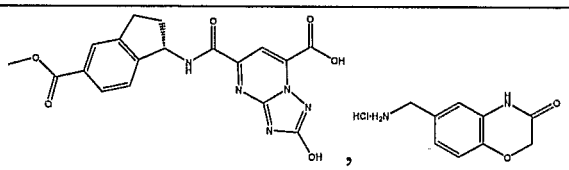
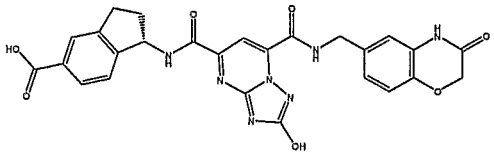
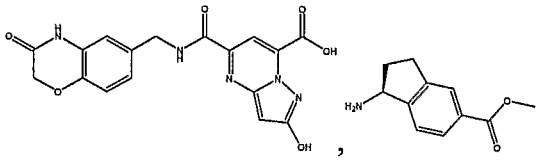
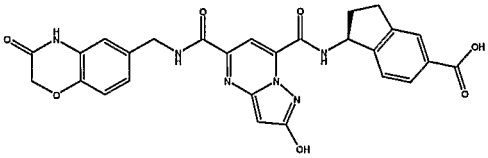
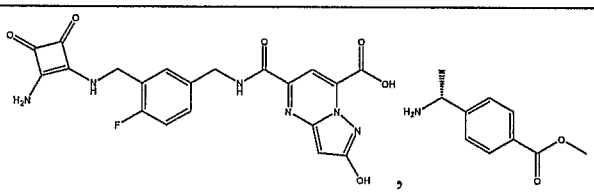
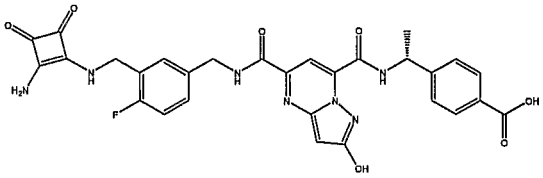
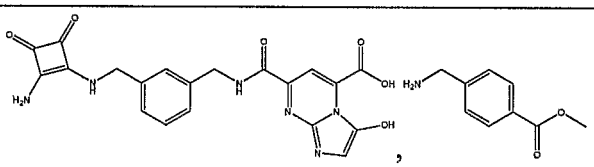
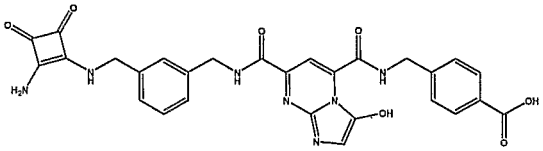
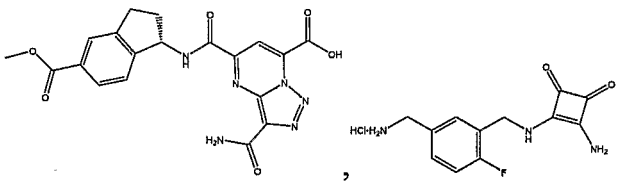
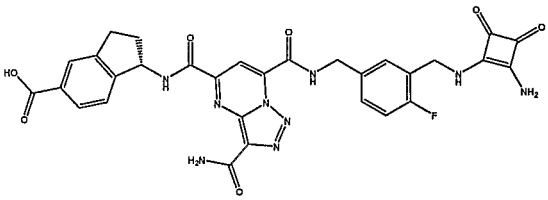
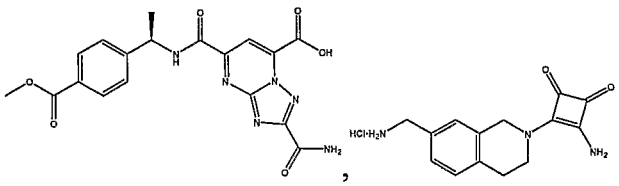
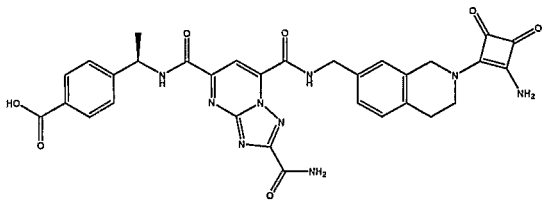
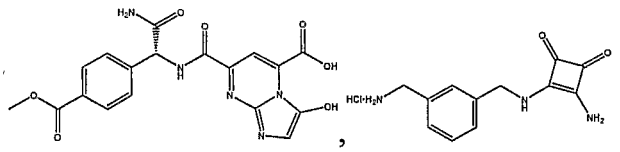
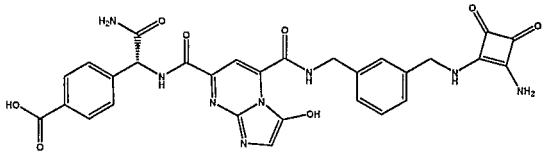
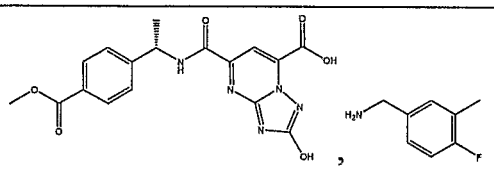
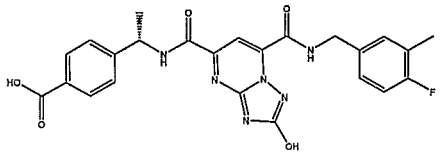
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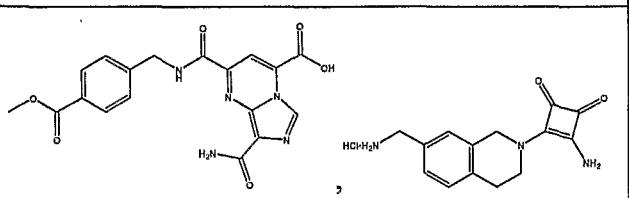
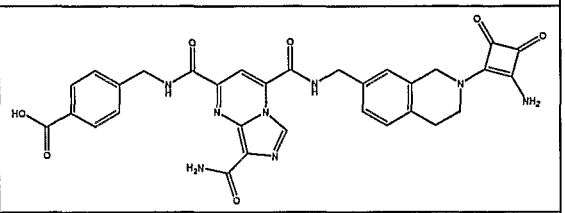
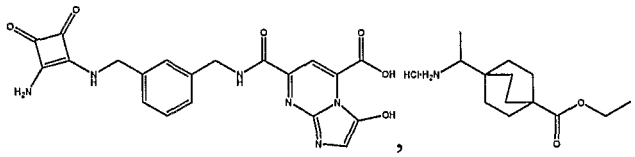
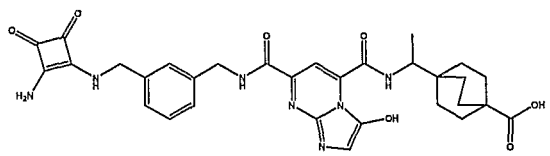
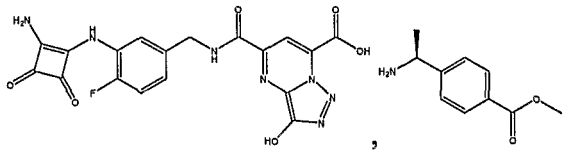
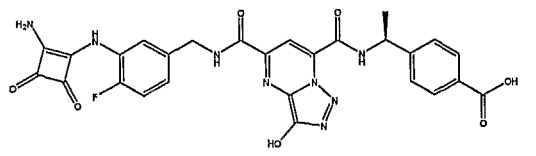
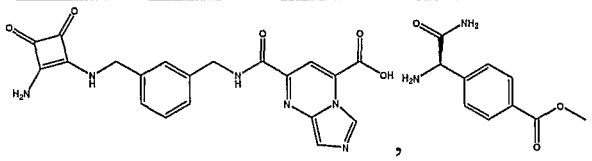
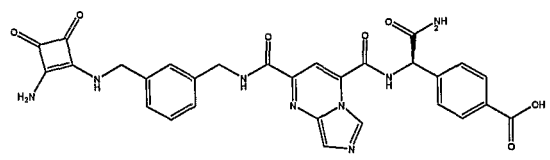
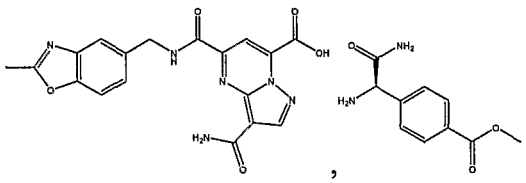
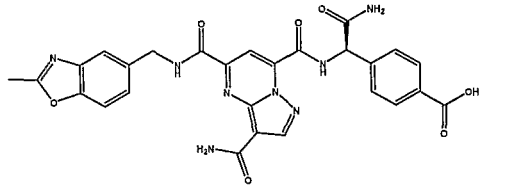
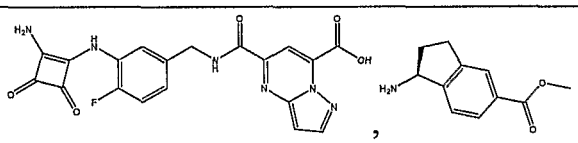
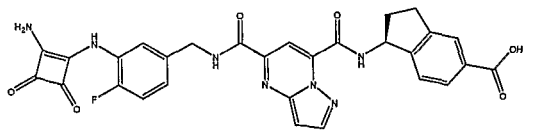
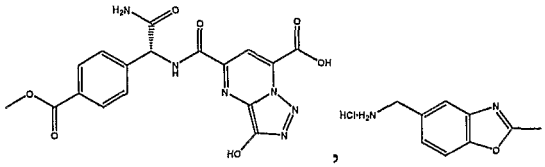
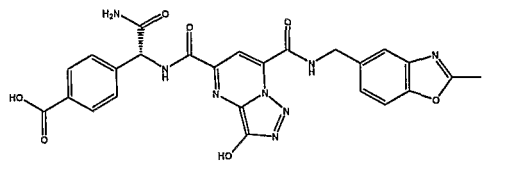
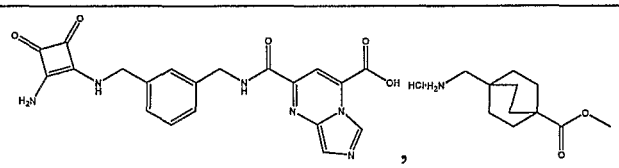
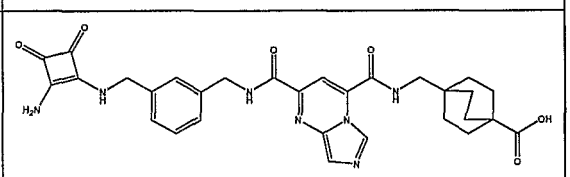
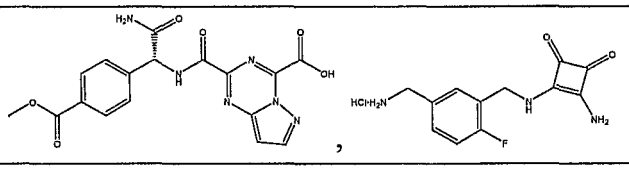
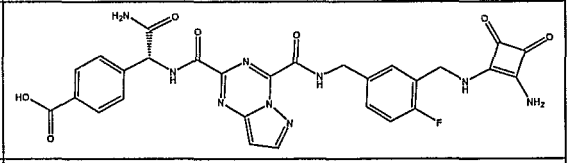
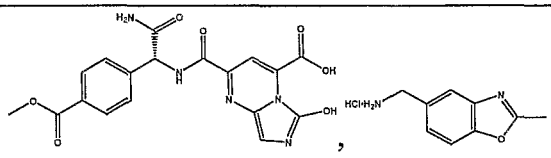
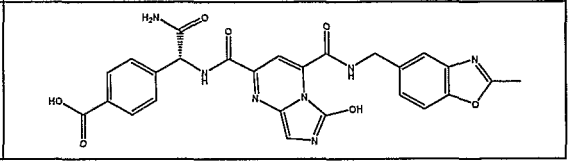
Examples 610-969

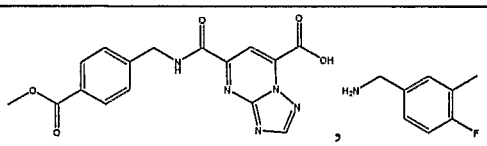
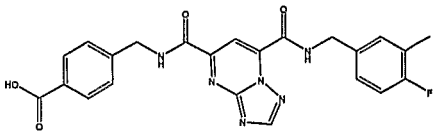
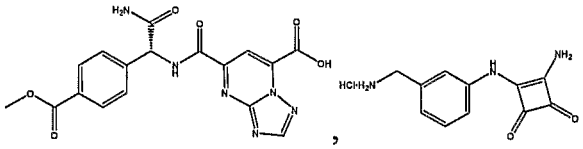
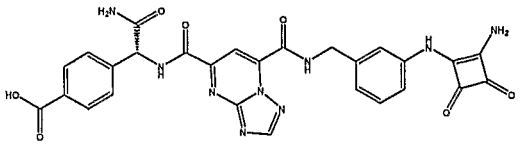
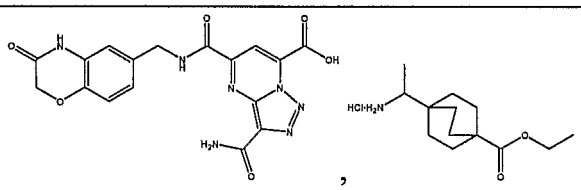
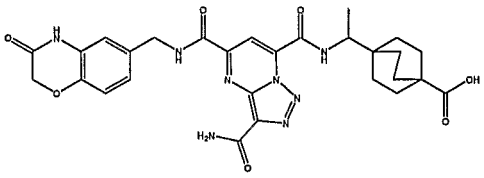
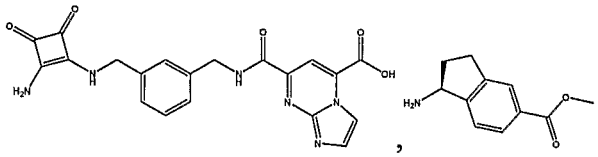
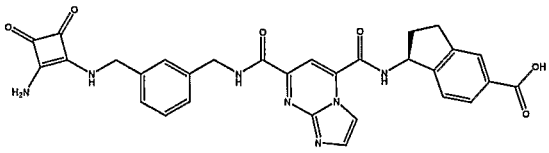
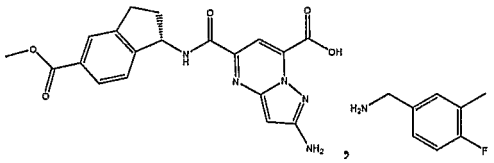
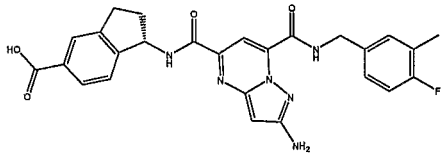
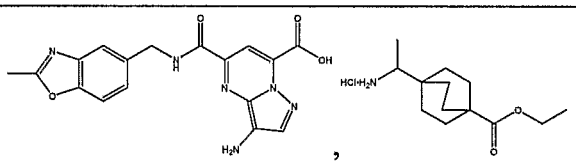
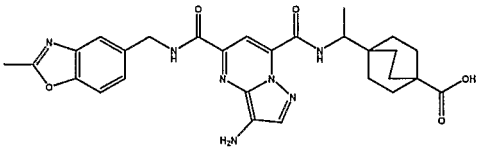
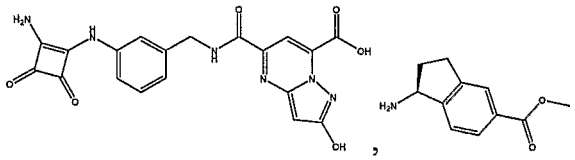
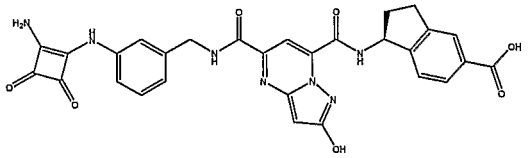
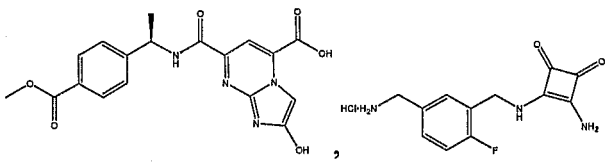
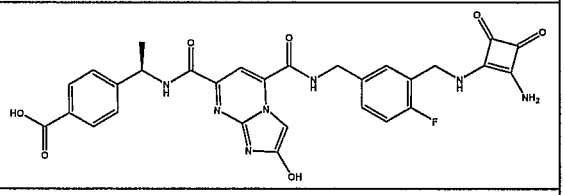
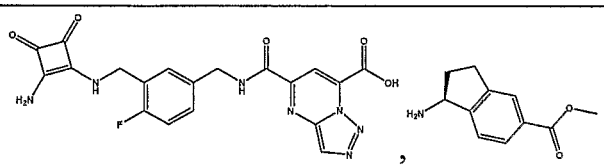
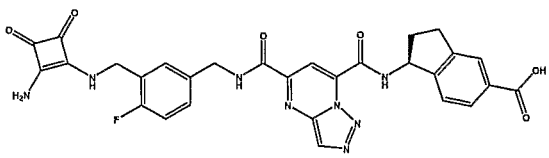
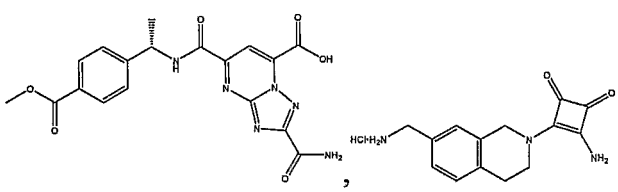
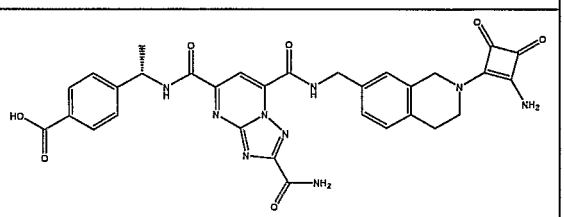
[0593] If one were to follow similar procedures as described in the Examples 1, 2, 3, 4, 5, 6 or 7, except using the acids and amines indicated in Table II-14 below, and if one were to treat the obtained esters similarly as described in the Examples 314 or 315, the following compounds would be obtained.

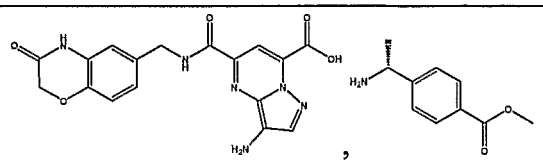
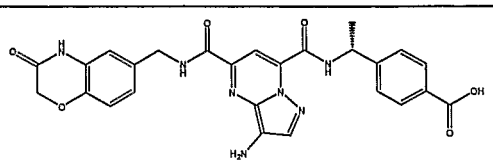
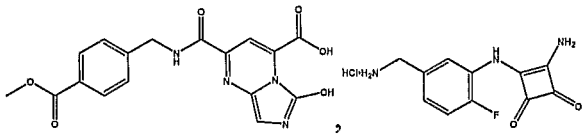
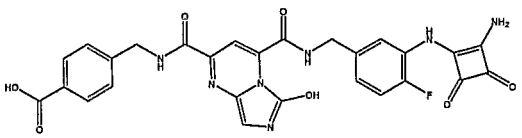
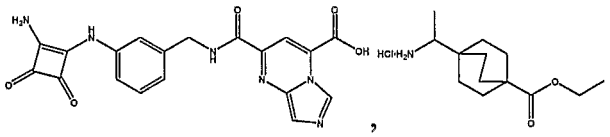
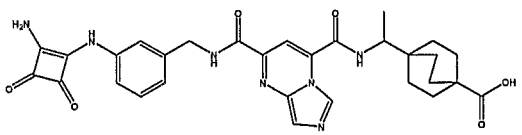
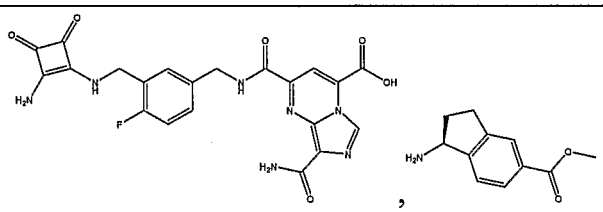
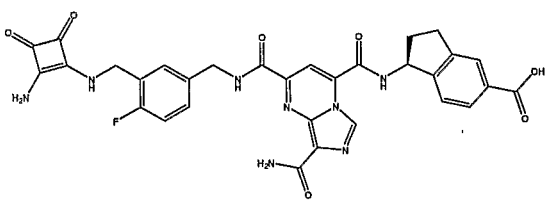
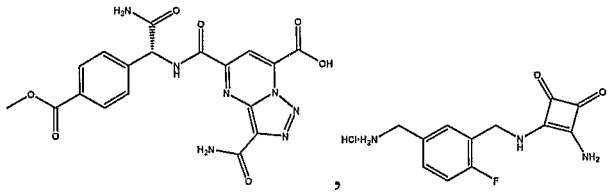
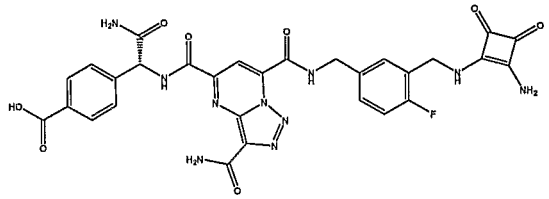
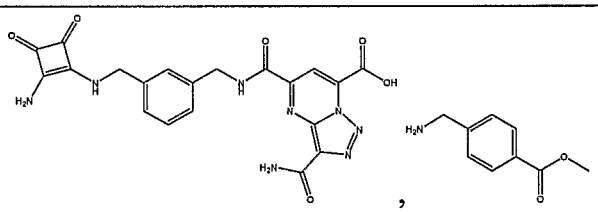
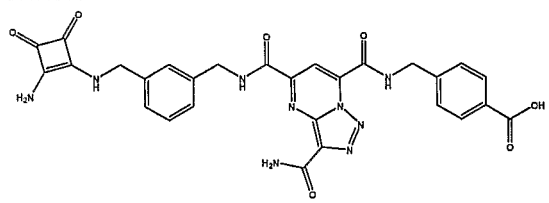
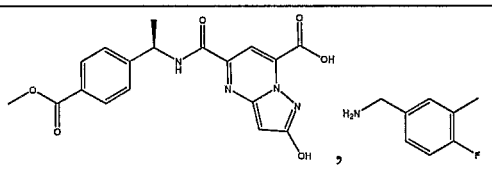
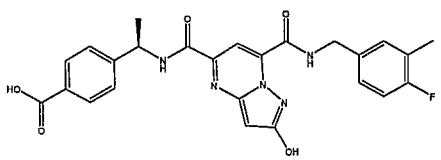
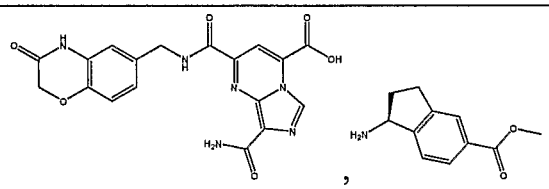
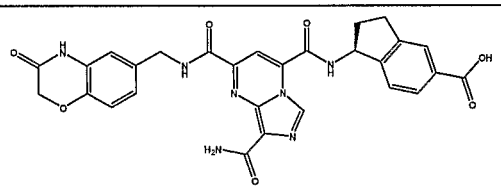
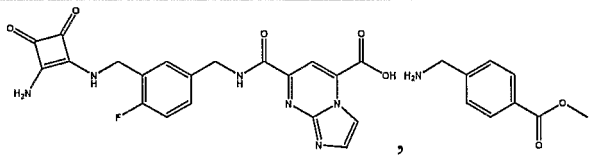
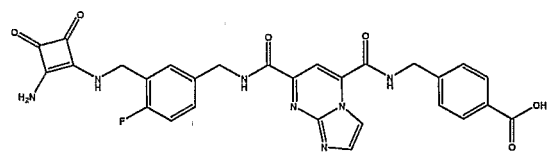
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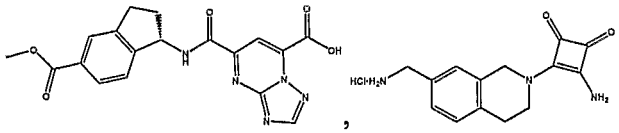
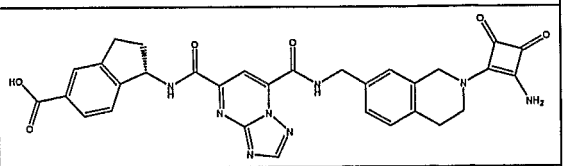
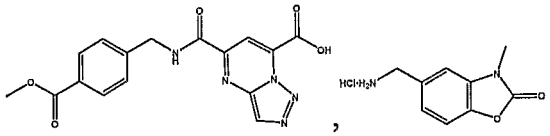
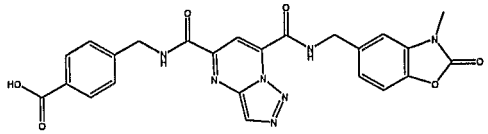
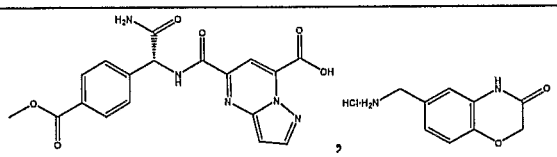
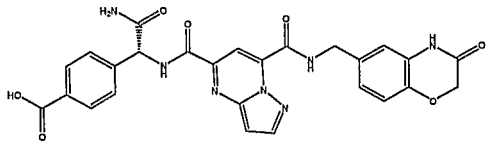
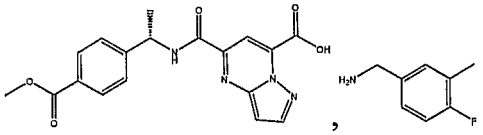
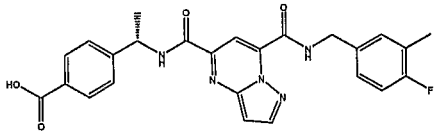
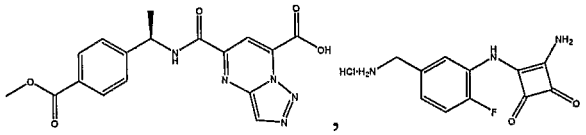
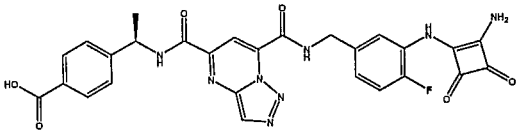
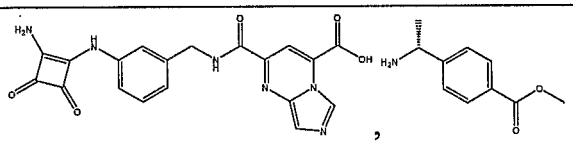
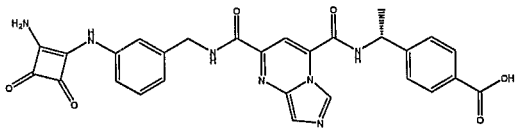
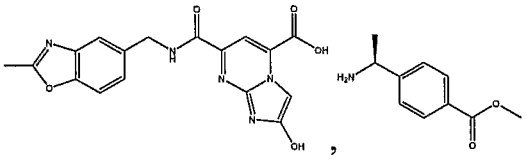
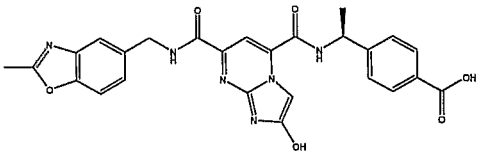
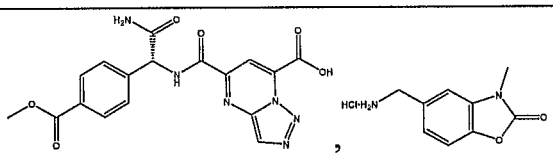
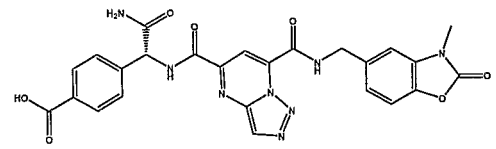
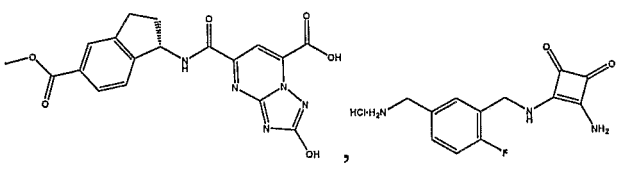
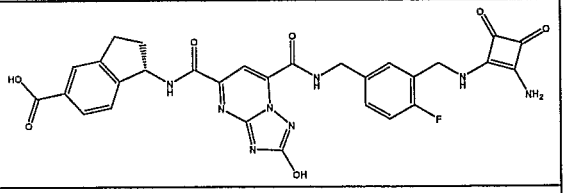
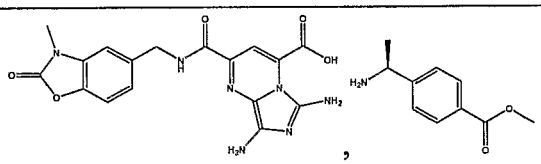
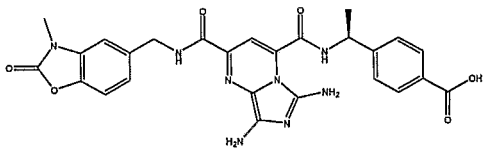
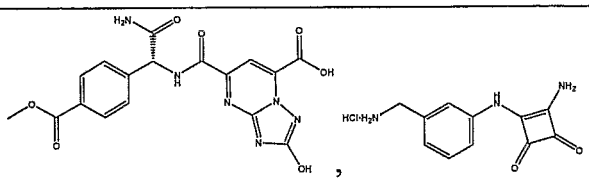
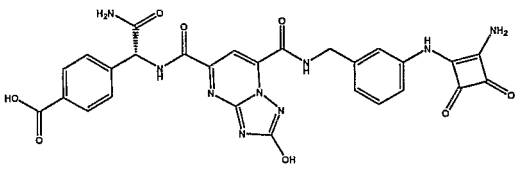
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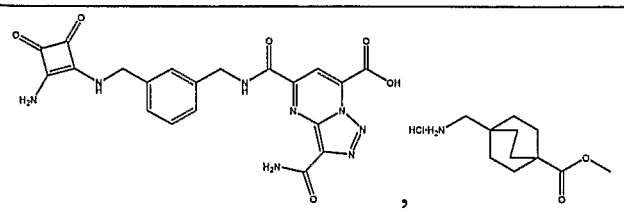
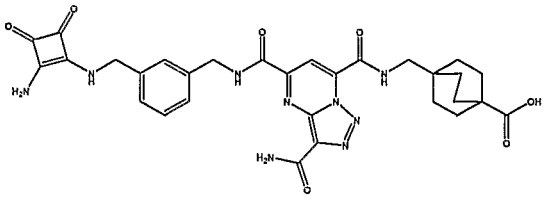
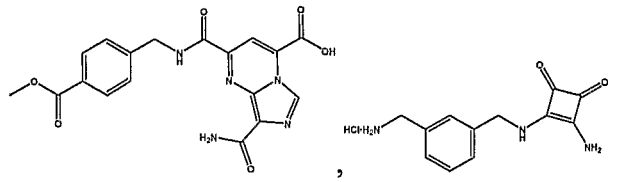
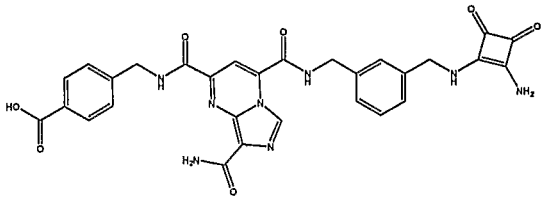
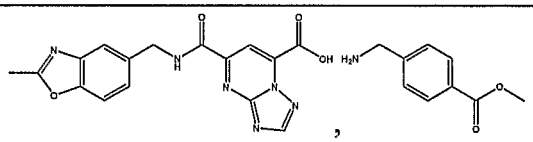
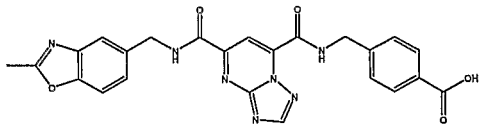
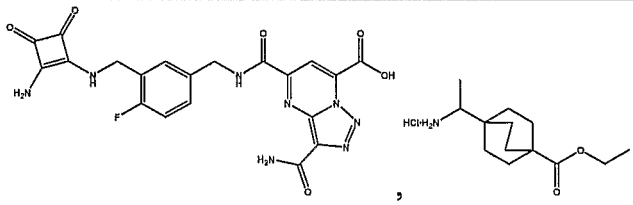
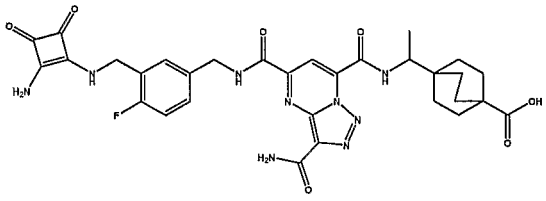
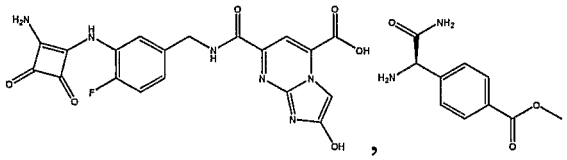
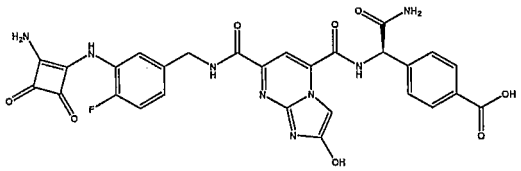
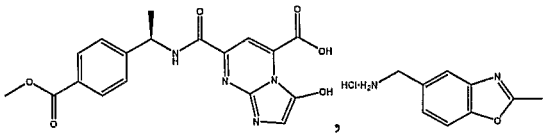
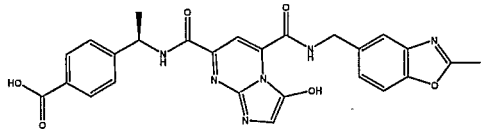
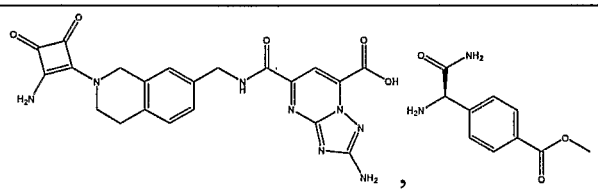
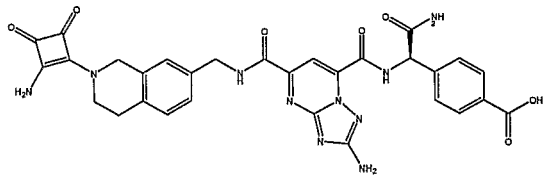
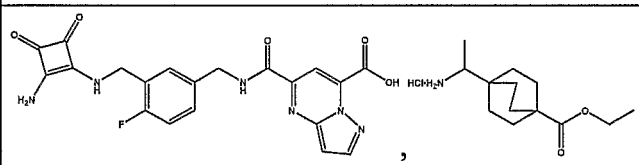
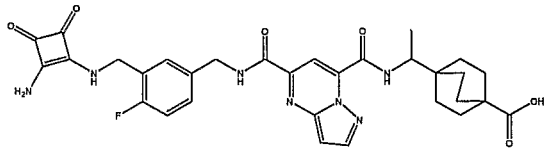
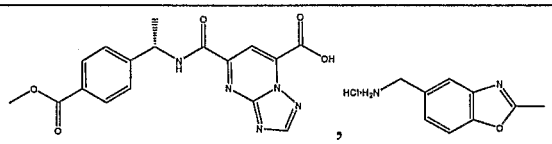
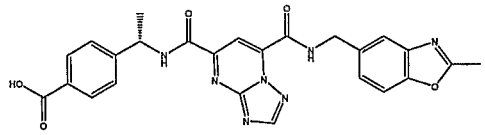
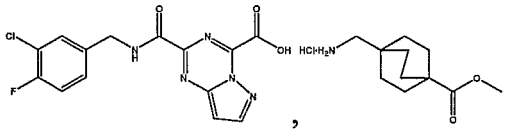
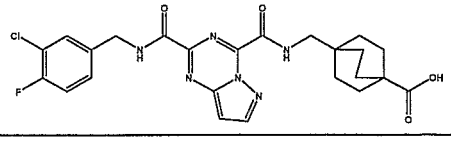
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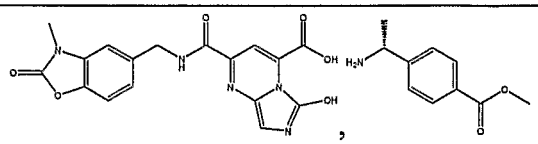
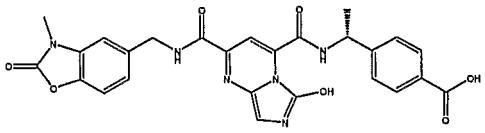
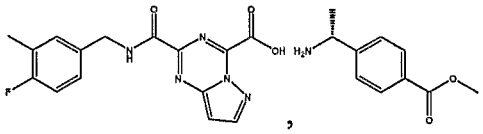
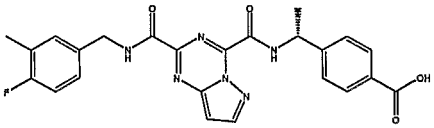
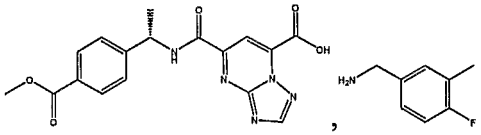
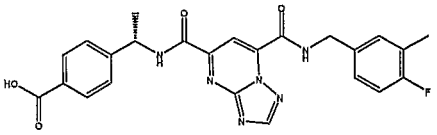
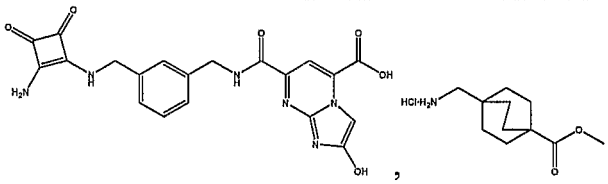
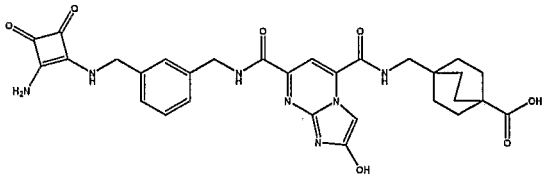
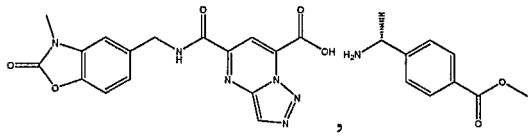
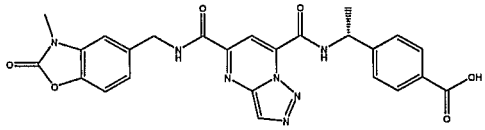
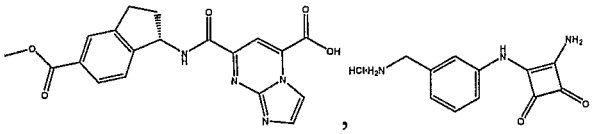
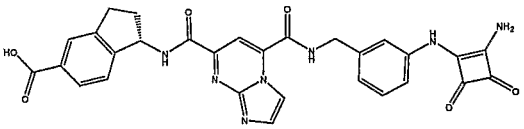
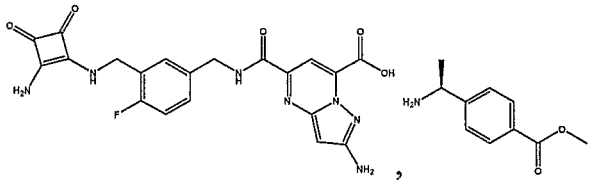
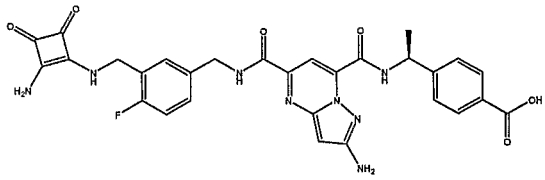
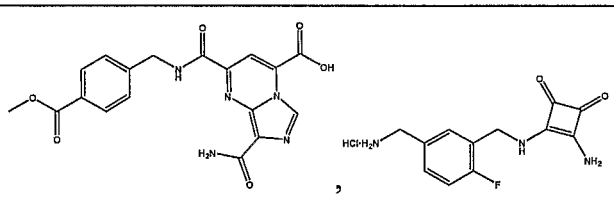
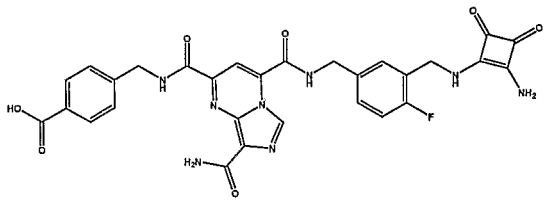
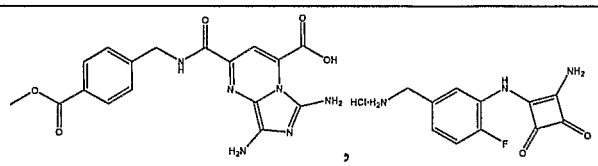
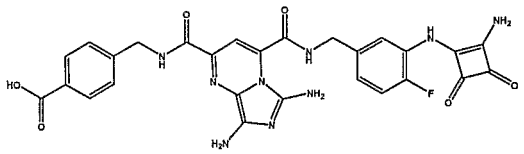
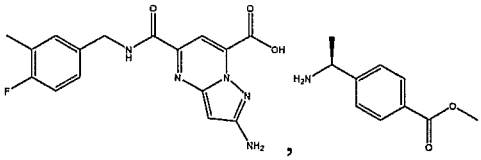
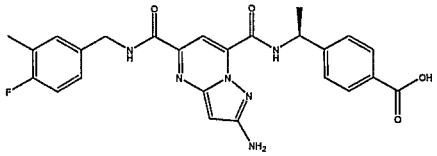
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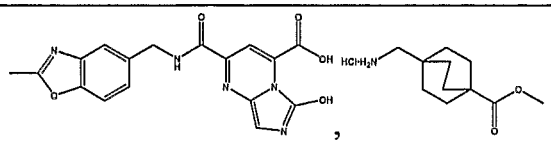
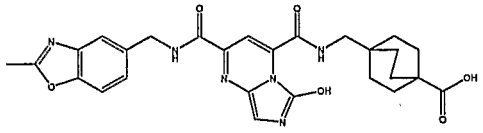
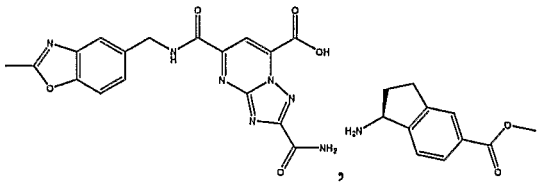
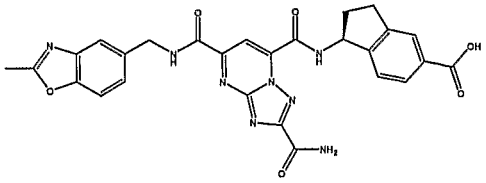
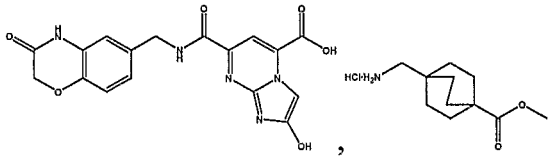
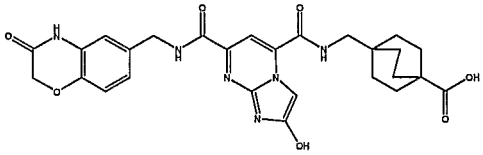
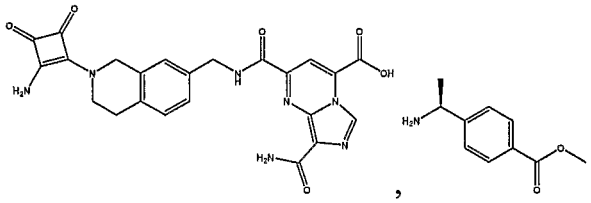
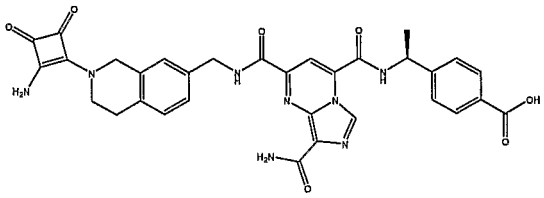
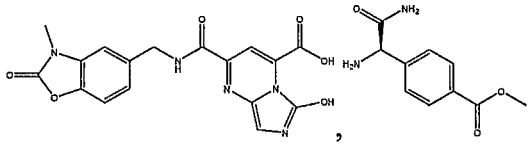
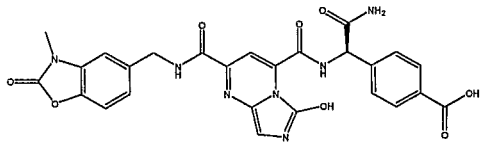
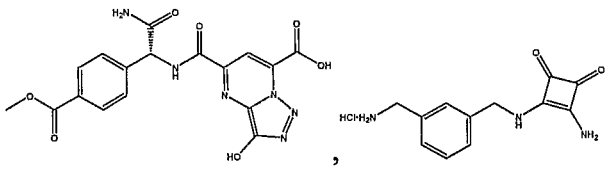
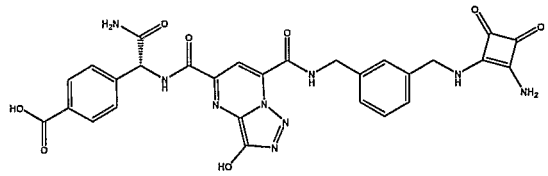
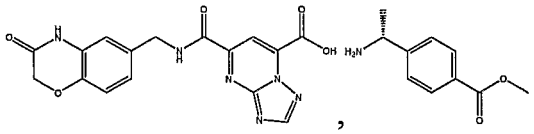
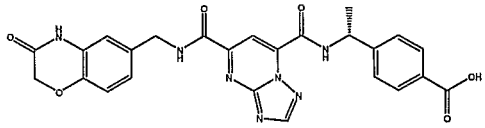
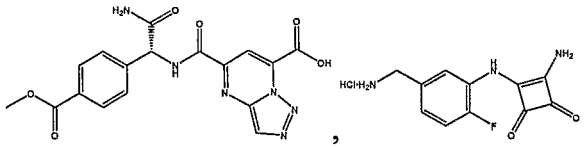
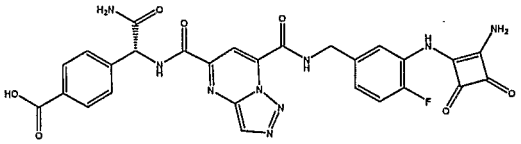
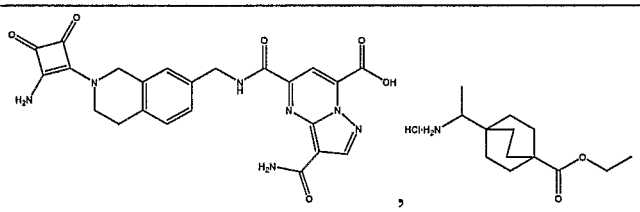
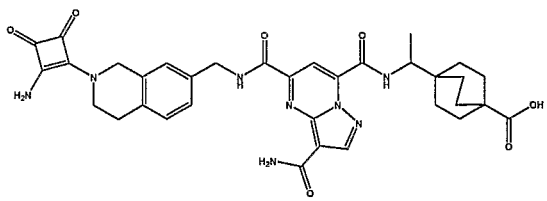
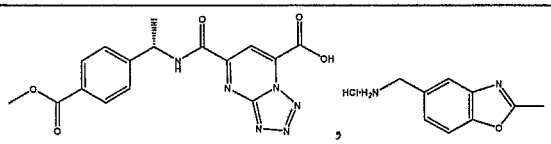
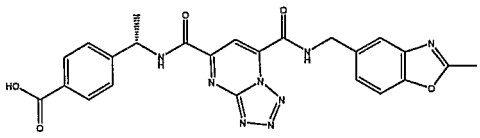
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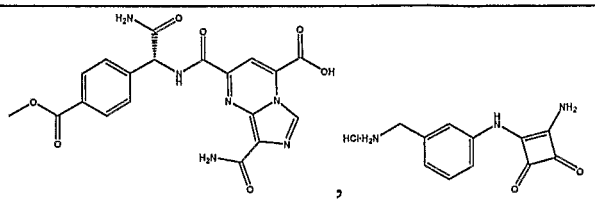
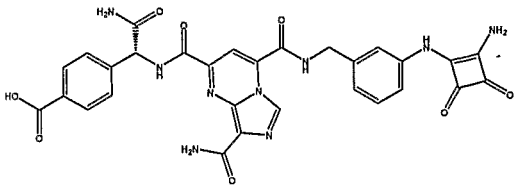
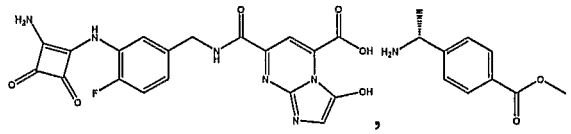
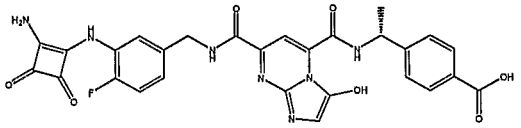
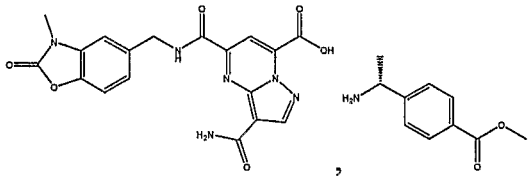
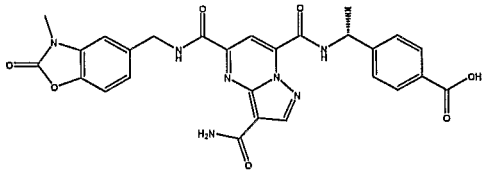
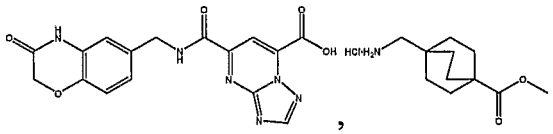
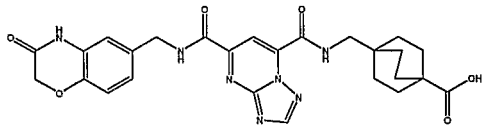
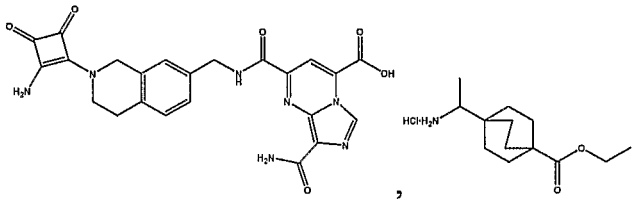
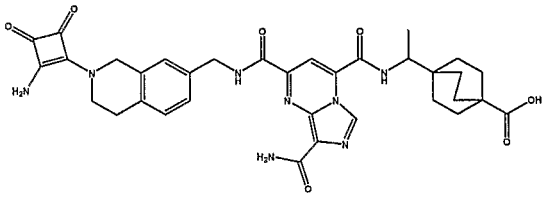
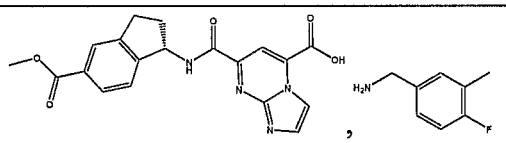
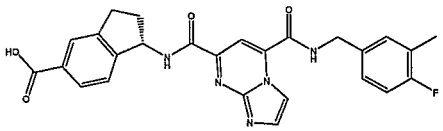
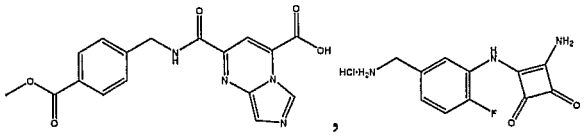
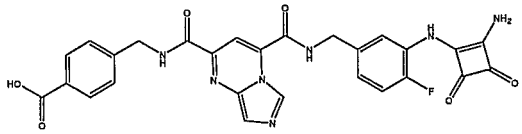
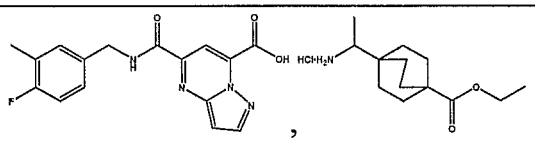
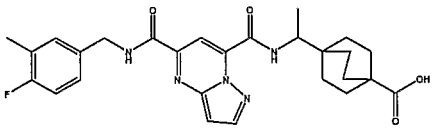
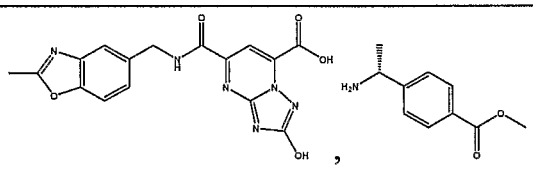
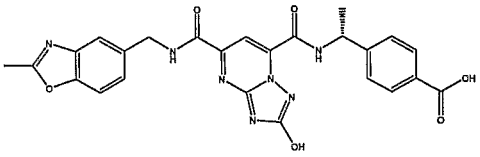
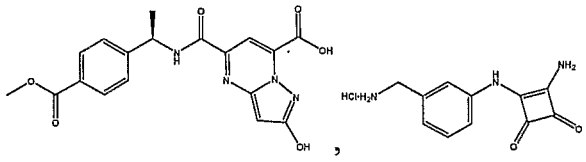
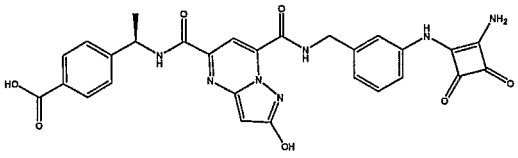
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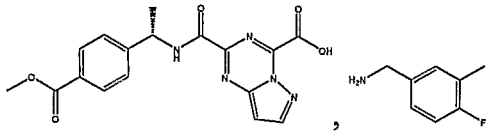
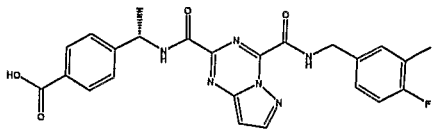
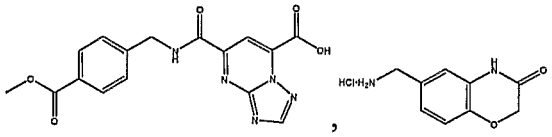
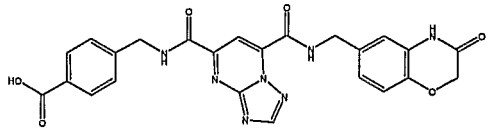
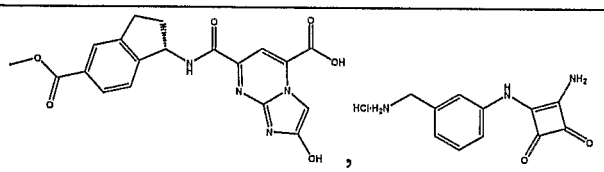
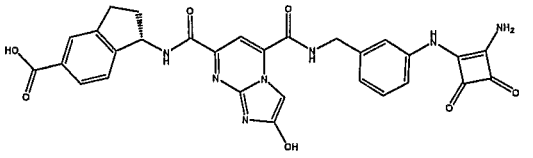
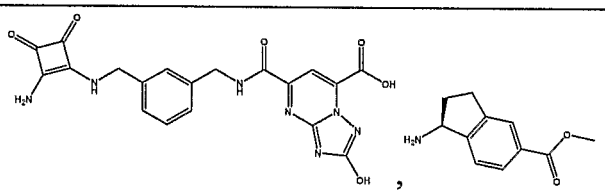
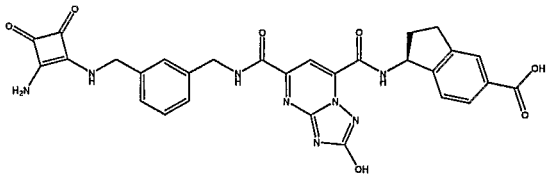
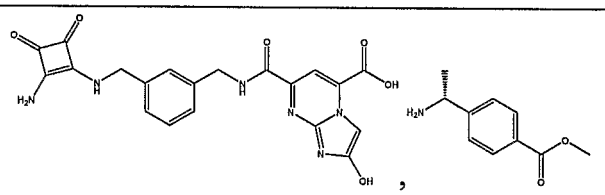
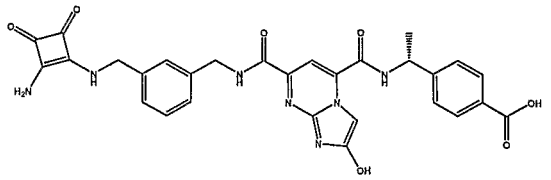
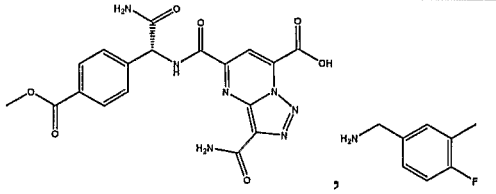
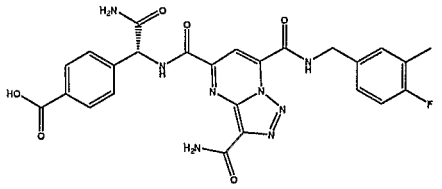
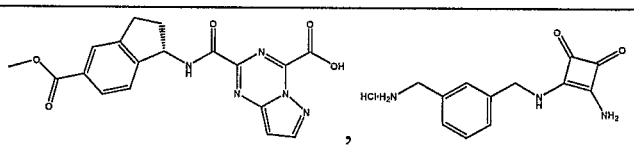
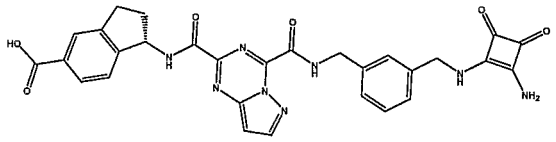
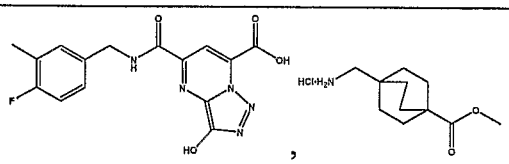
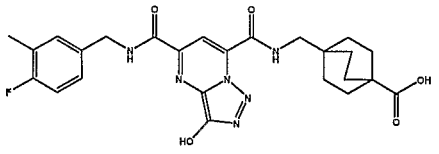
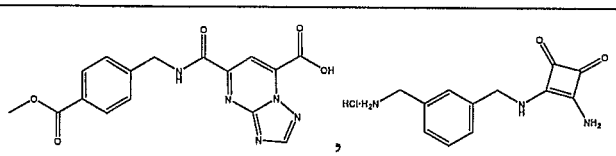
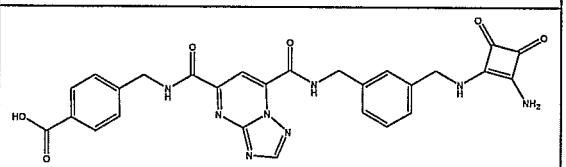
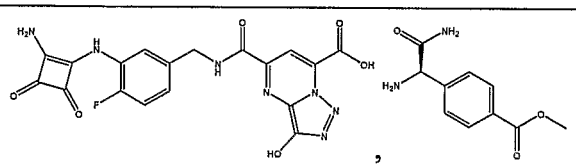
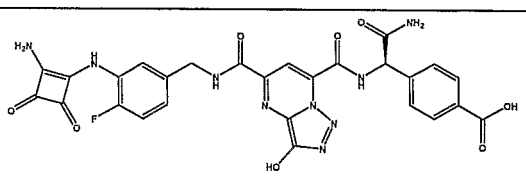
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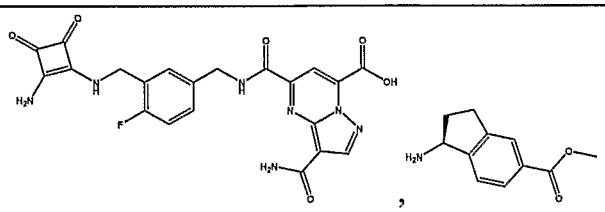
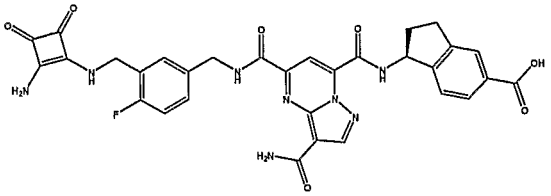
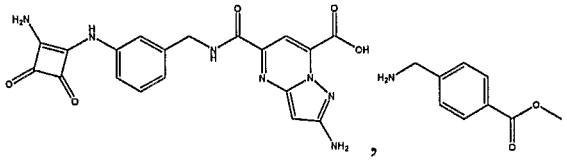
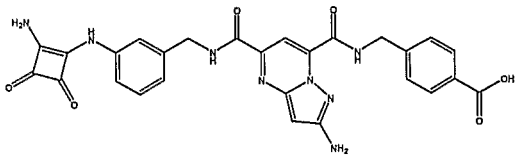
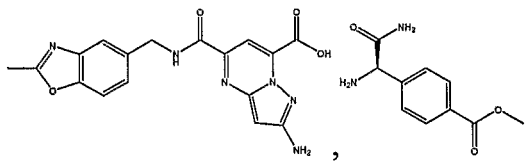
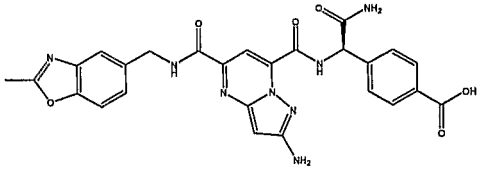
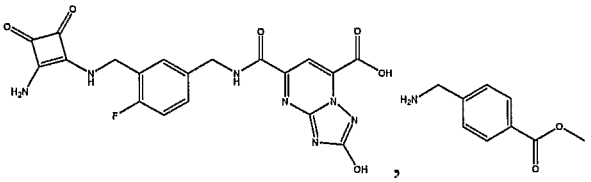
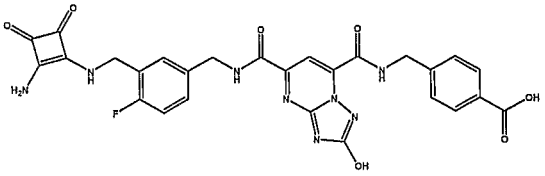
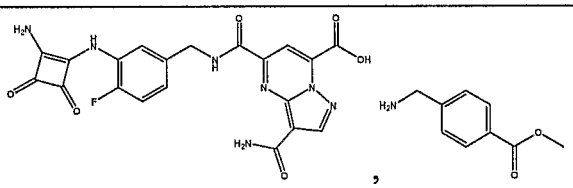
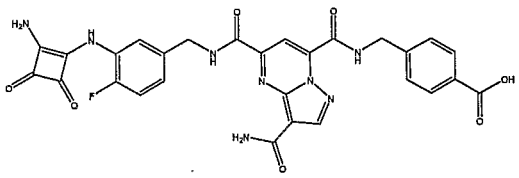
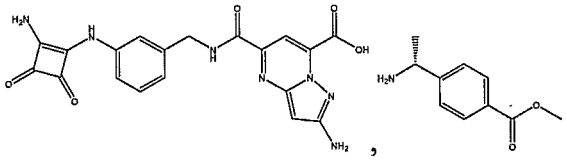
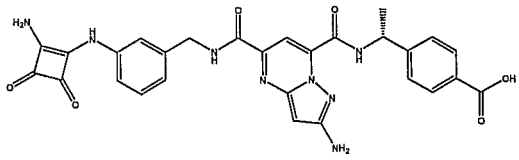
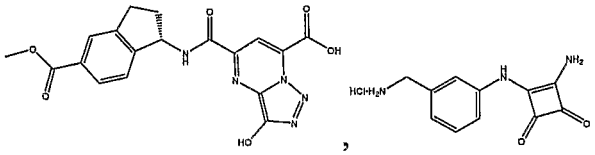
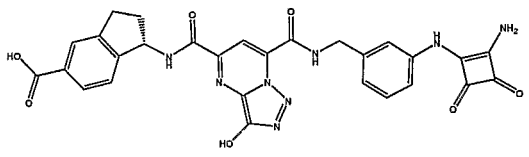
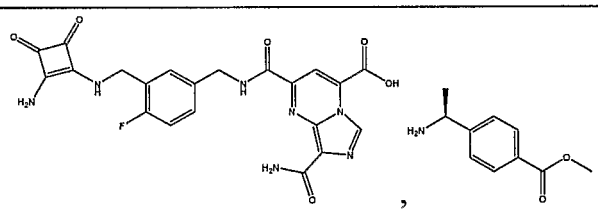
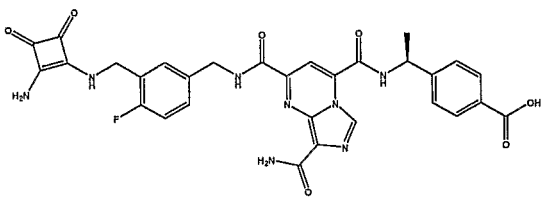
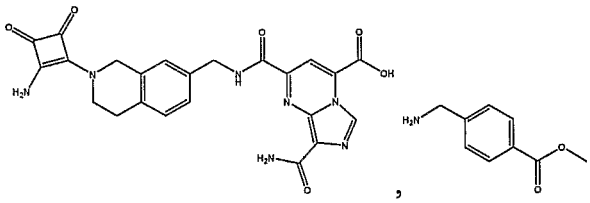
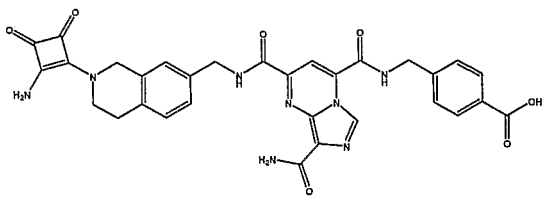
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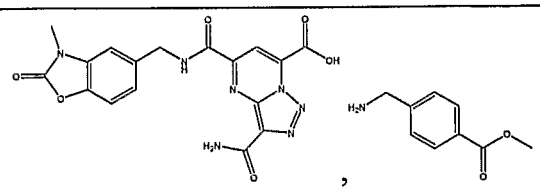
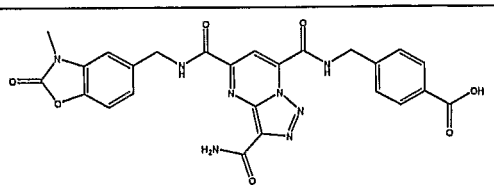
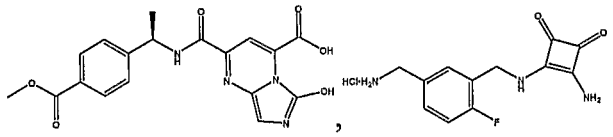
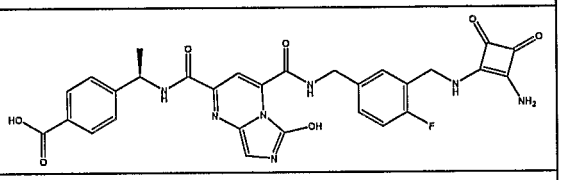
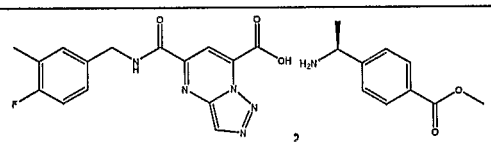
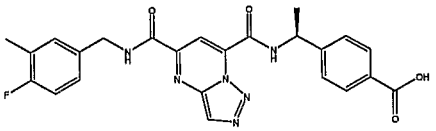
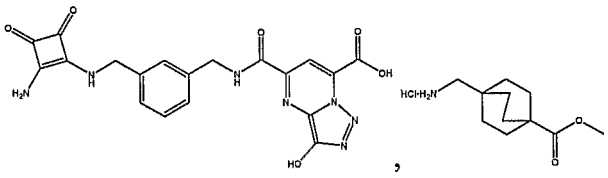
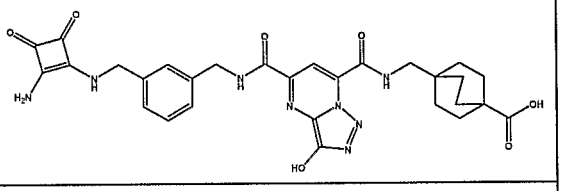
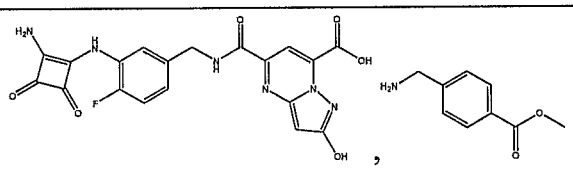
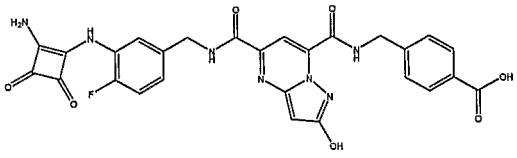
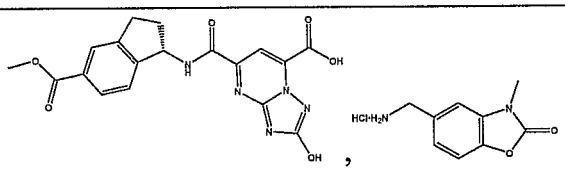
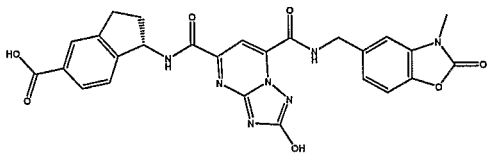
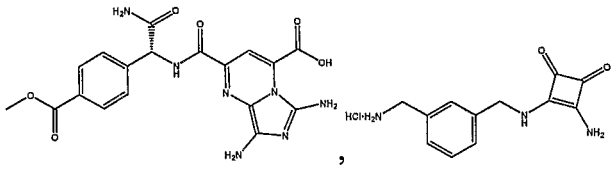
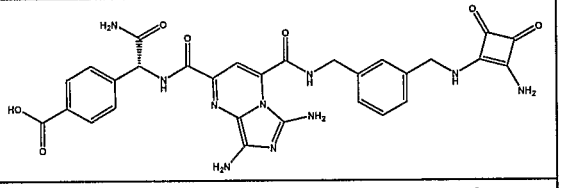
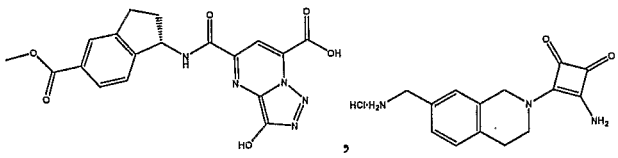
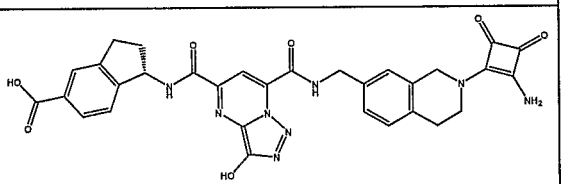
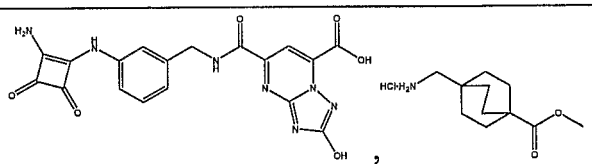
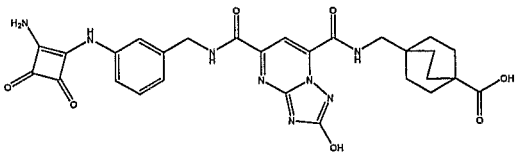
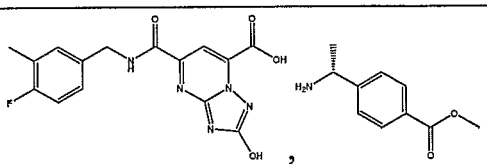
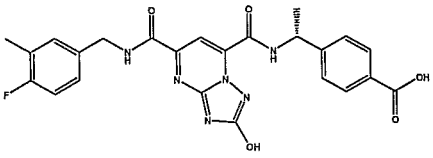
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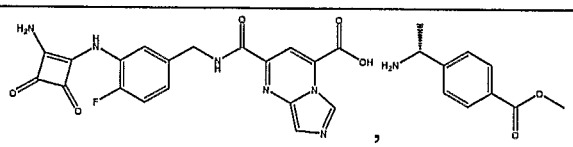
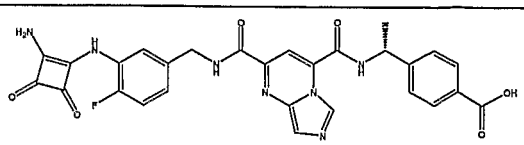
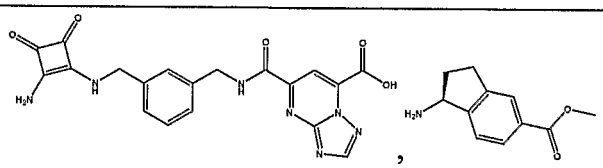
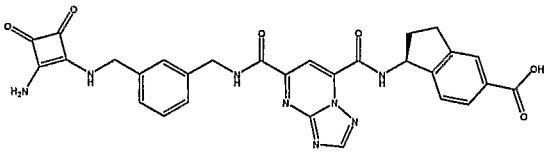
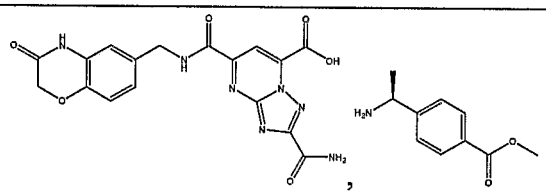
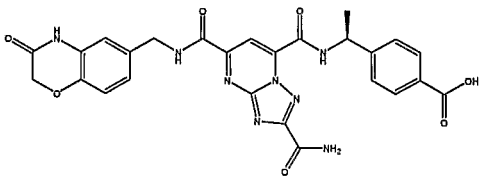
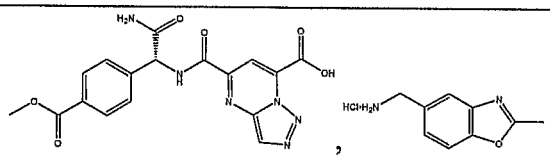
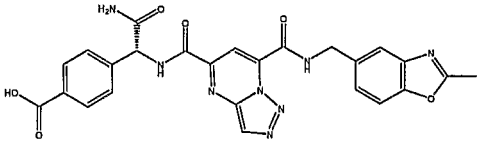
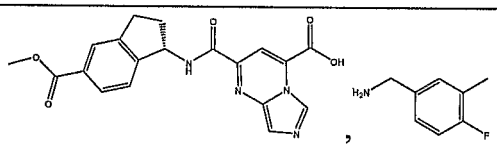
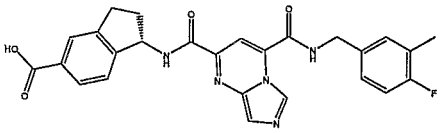
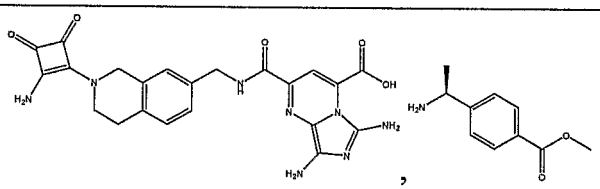
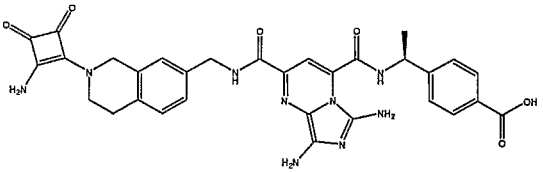
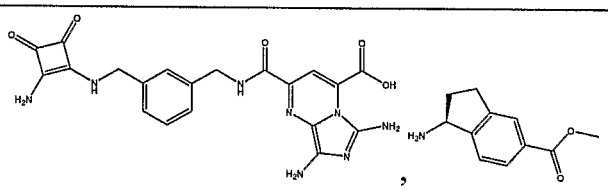
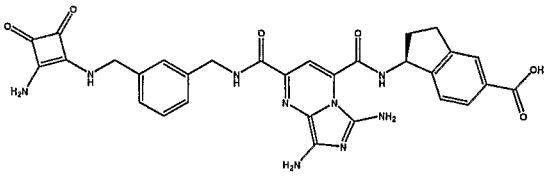
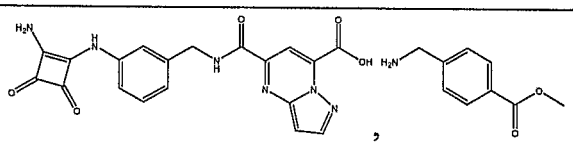
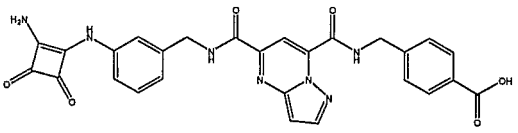
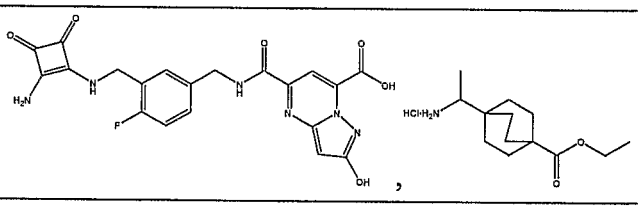
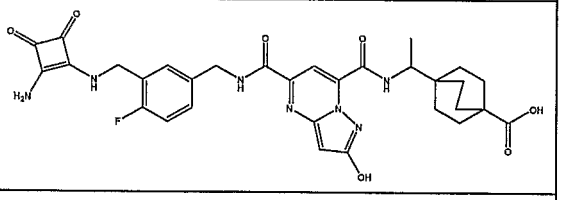
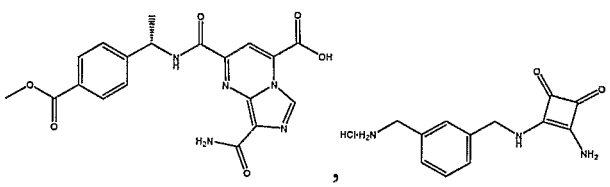
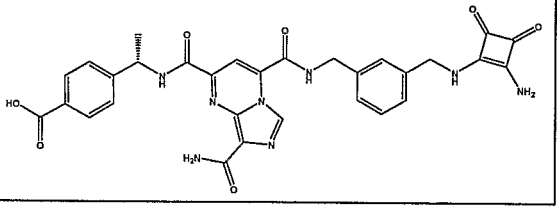
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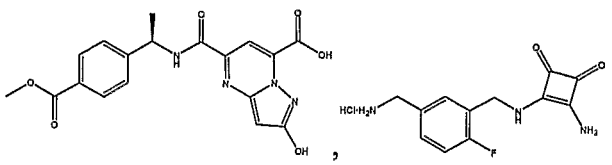
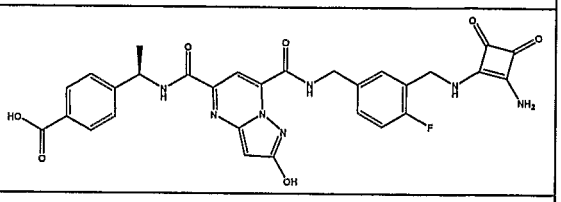
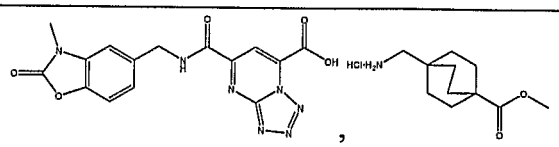
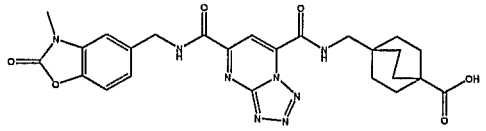
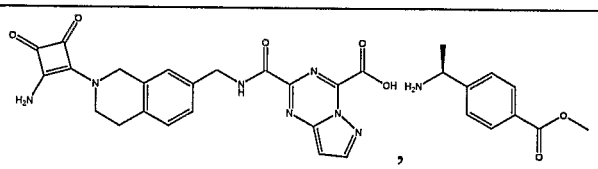
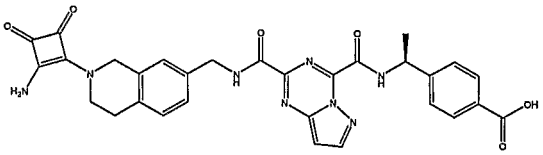
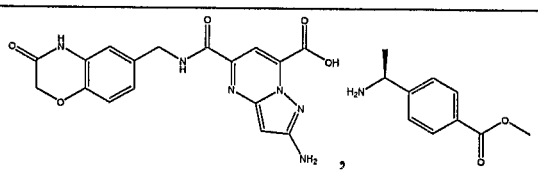
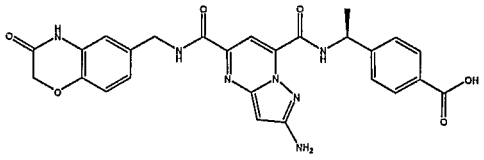
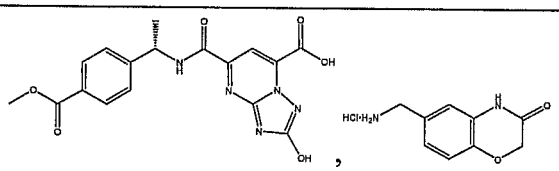
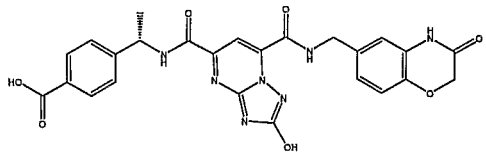
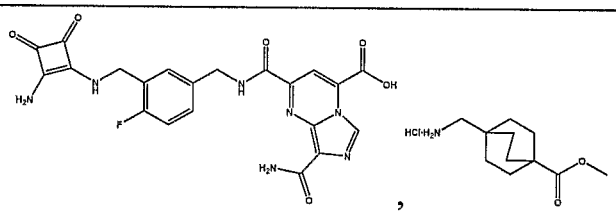
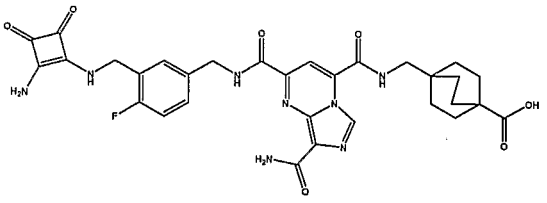
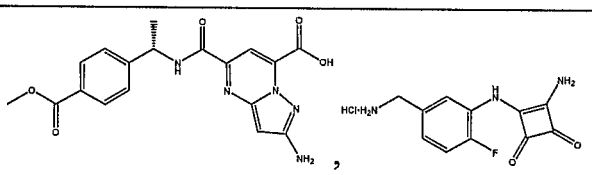
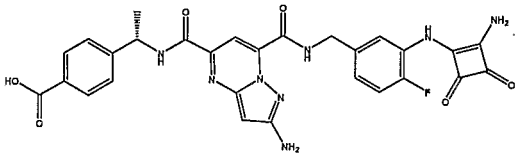
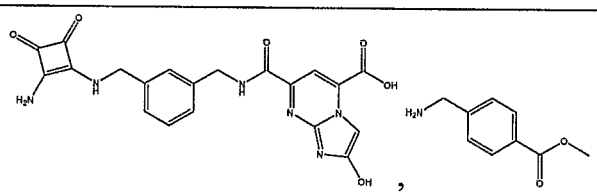
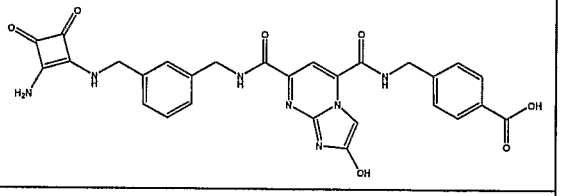
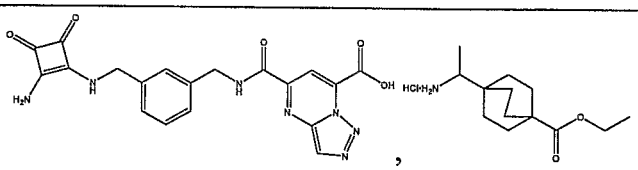
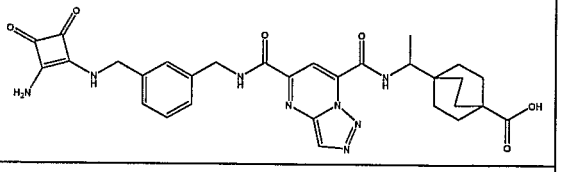
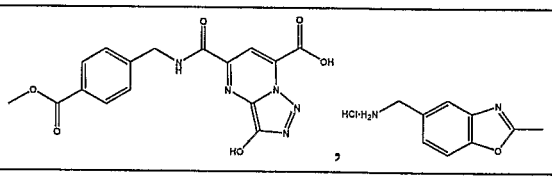
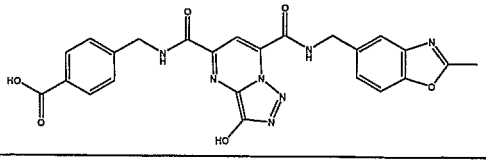
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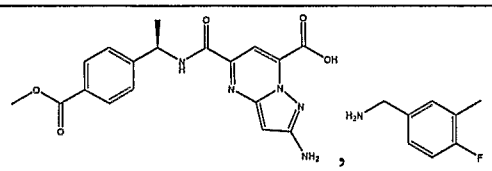
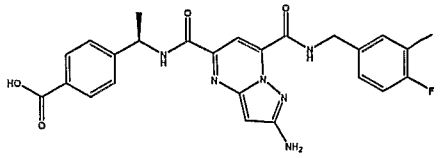
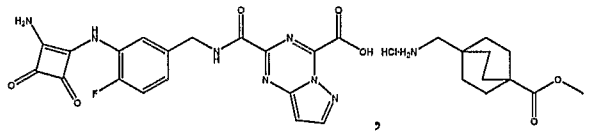
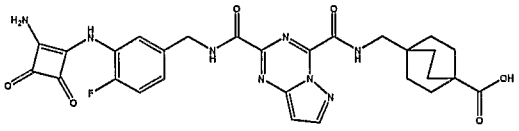
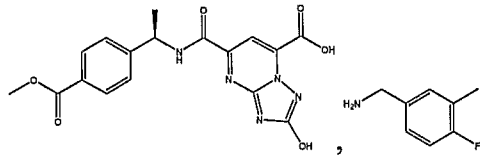
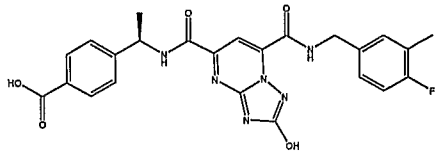
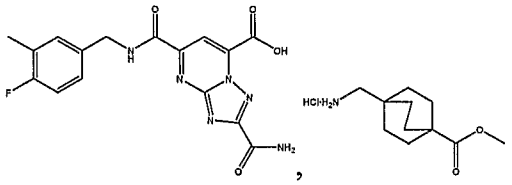
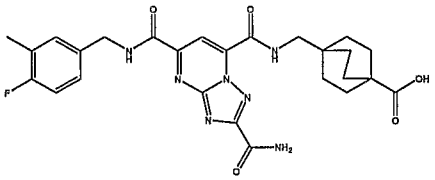
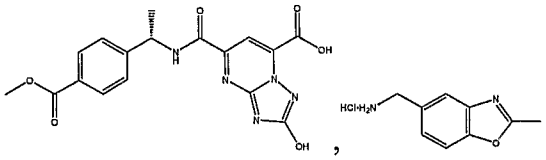
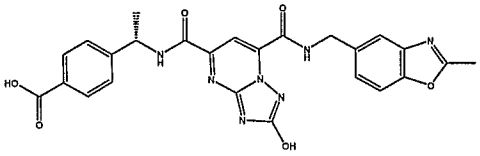
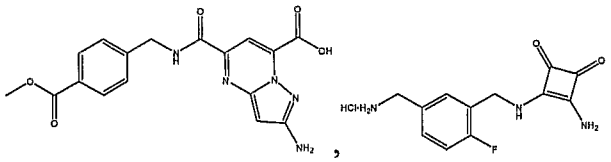
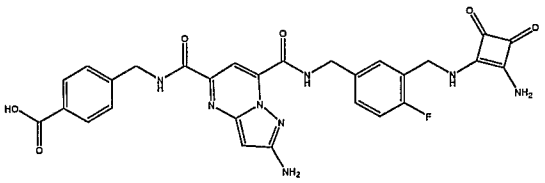
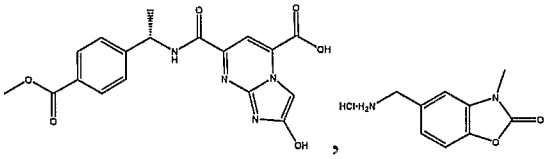
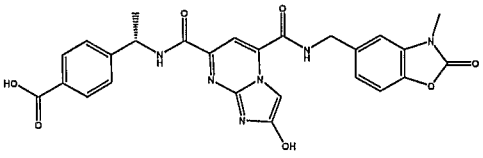
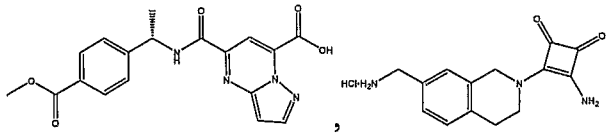
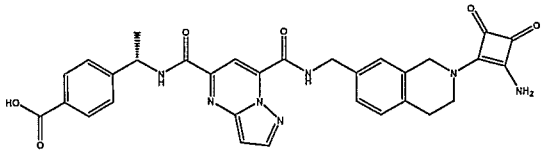
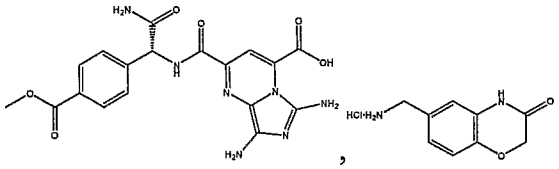
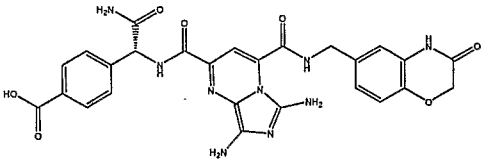
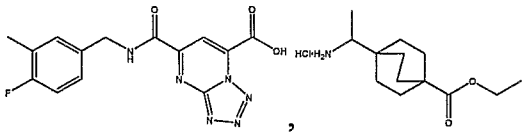
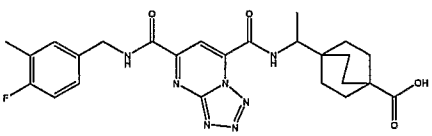
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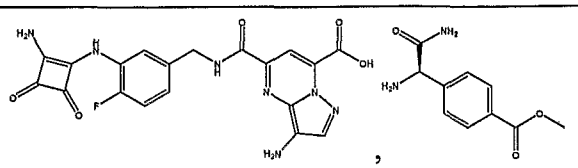
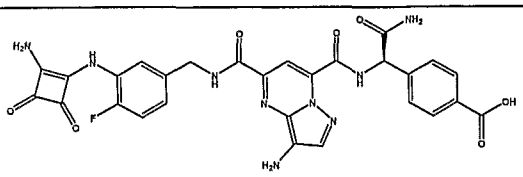
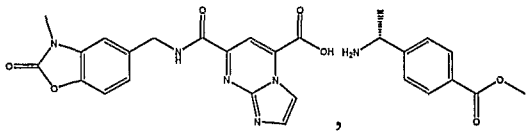
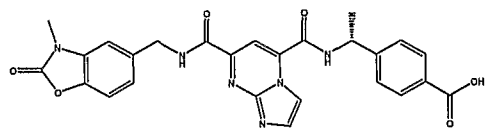
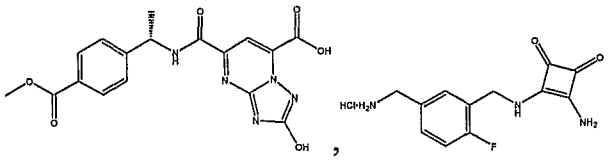
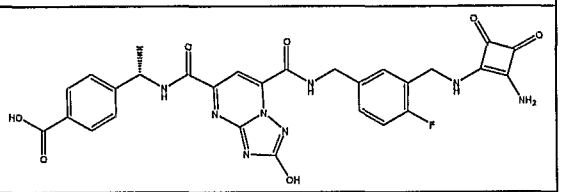
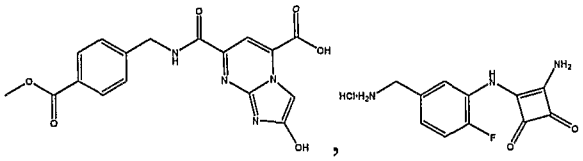
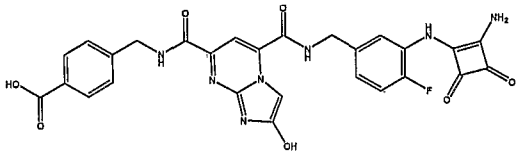
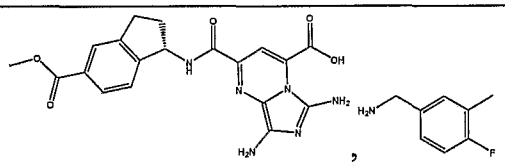
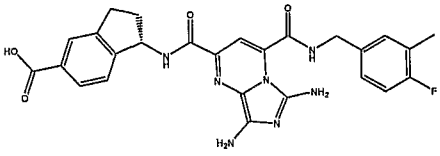
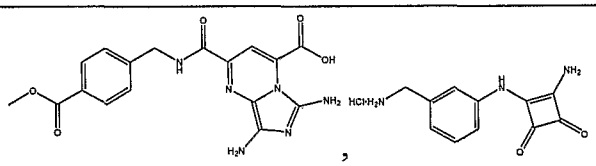
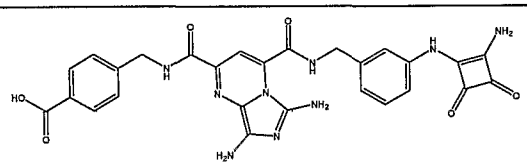
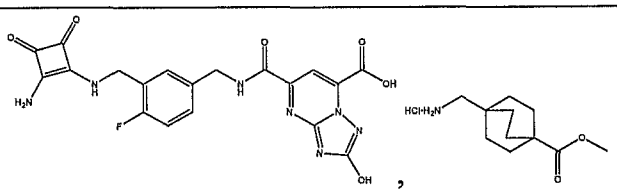
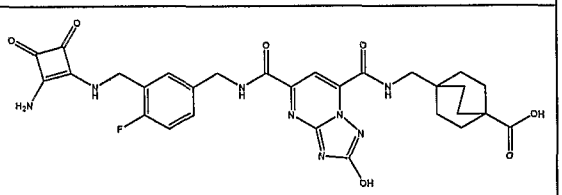
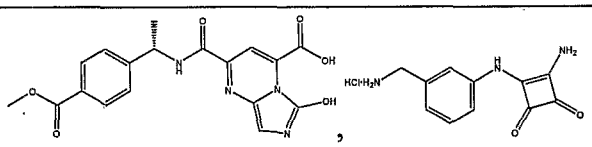
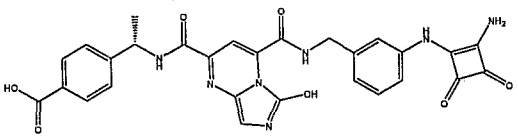
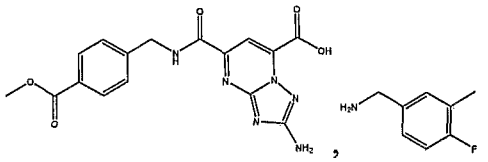
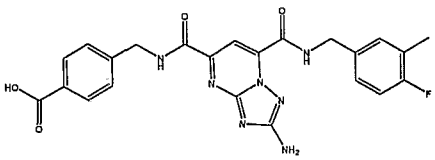
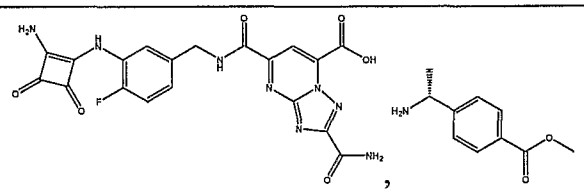
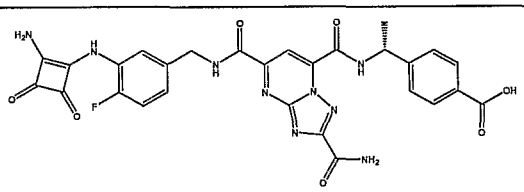
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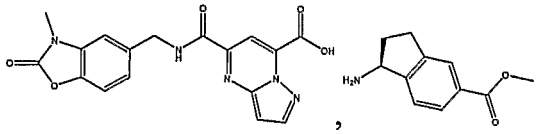
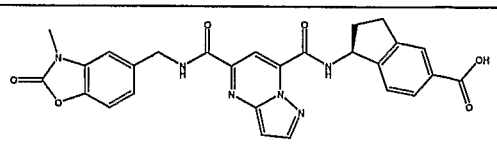
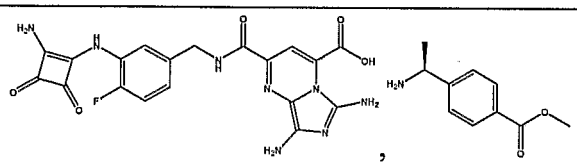
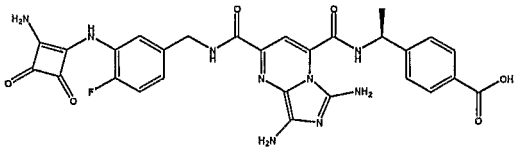
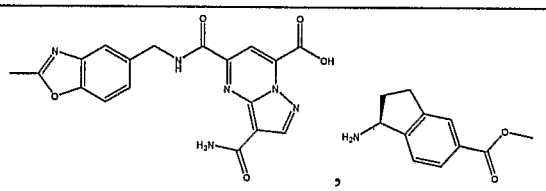
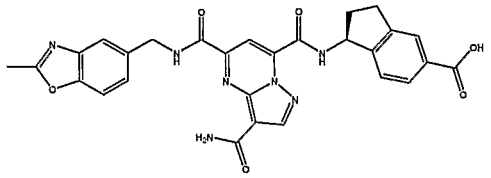
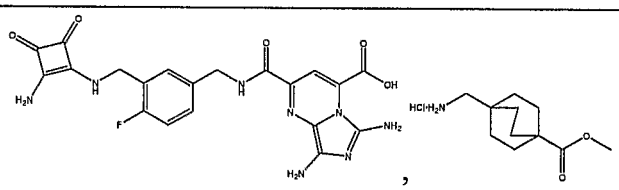
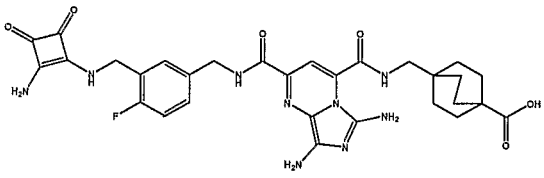
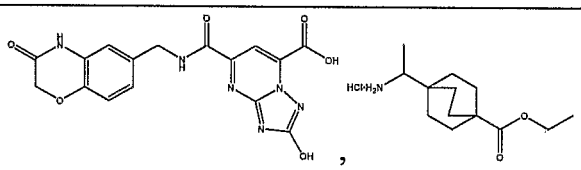
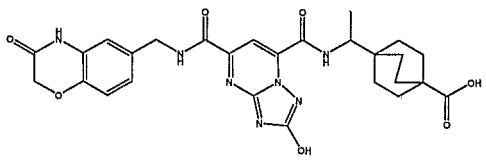
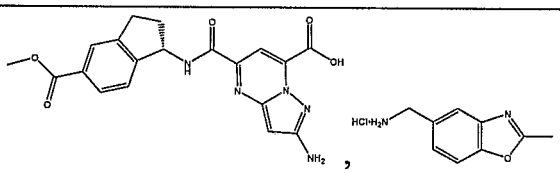
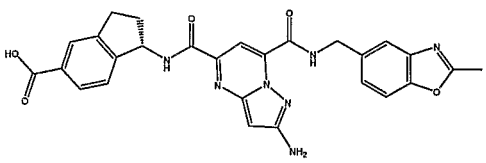
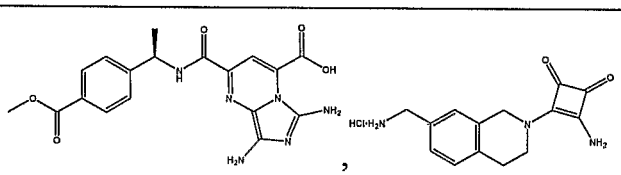
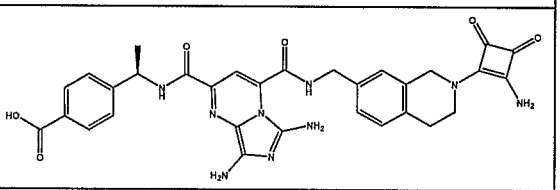
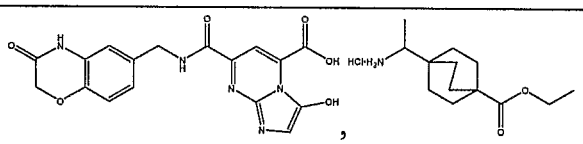
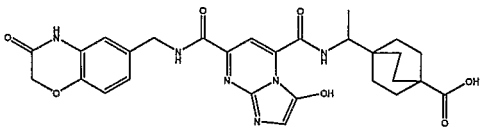
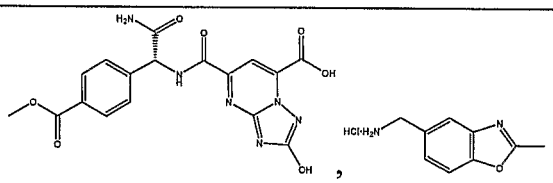
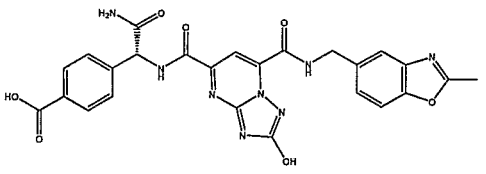
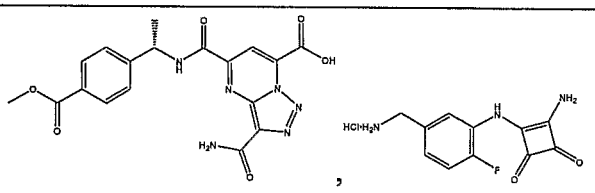
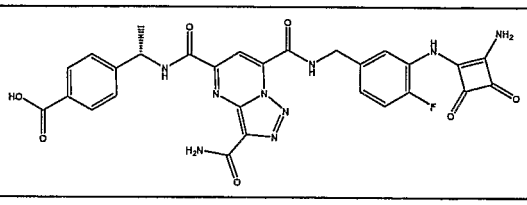
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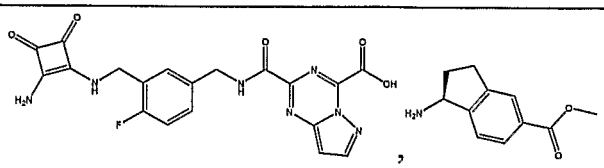
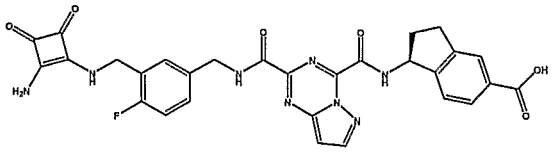
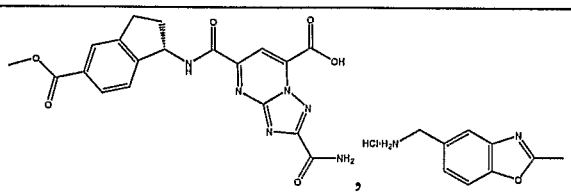
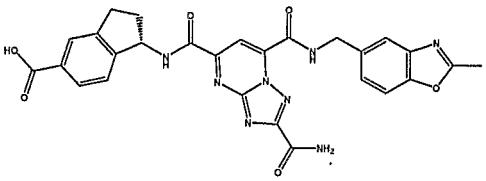
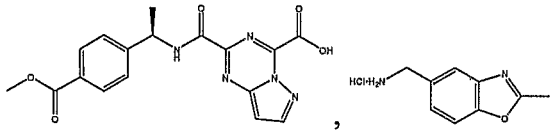
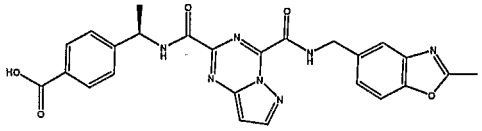
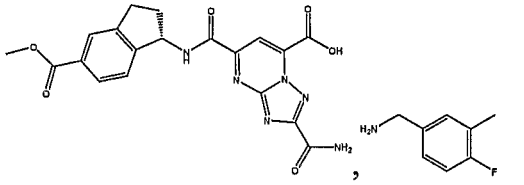
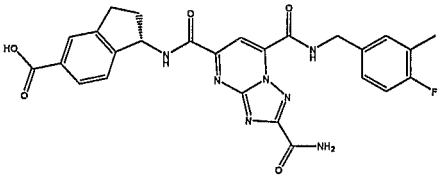
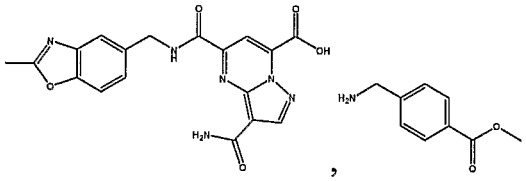
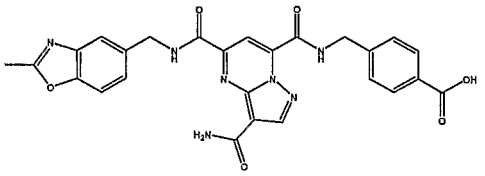
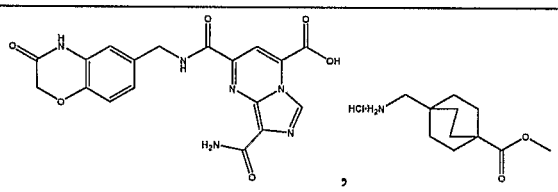
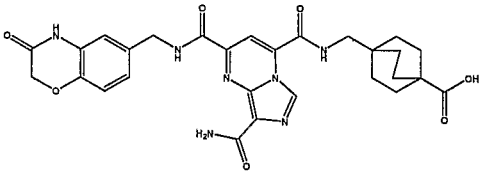
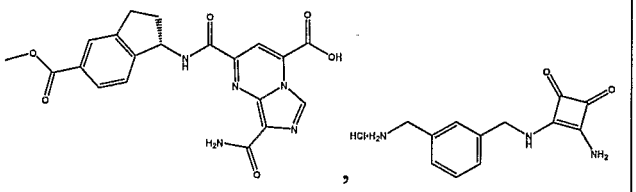
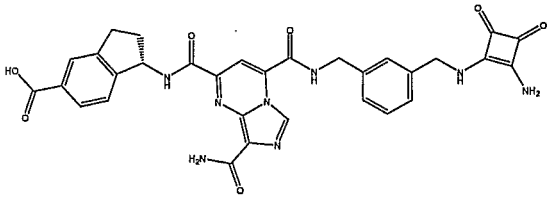
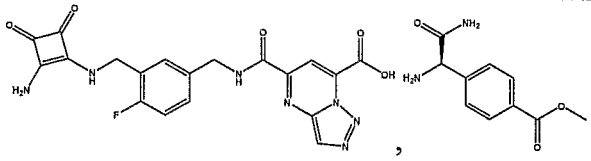
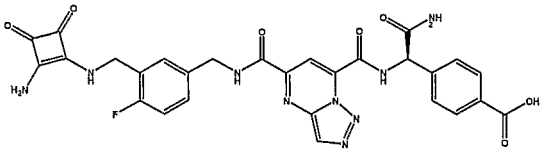
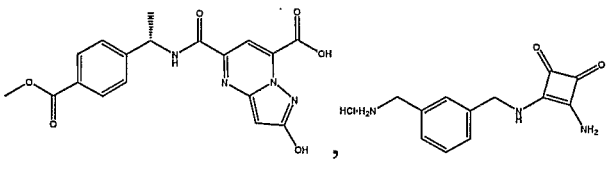
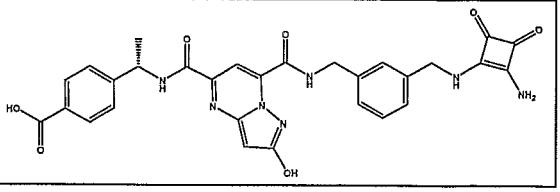
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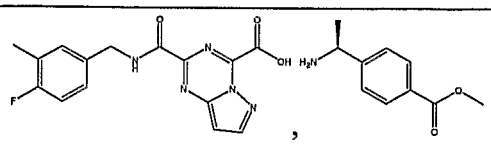
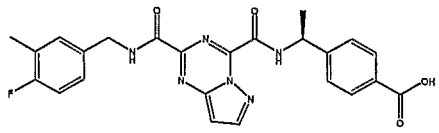
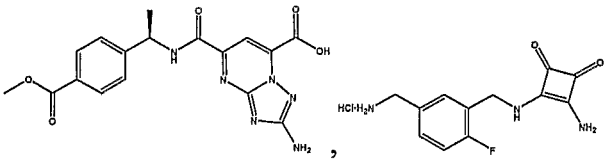
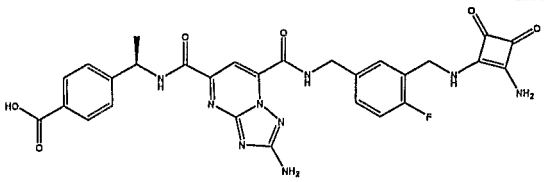
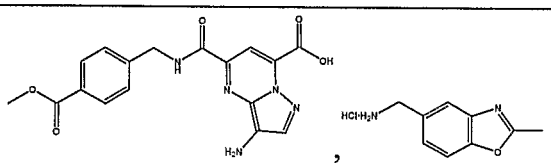
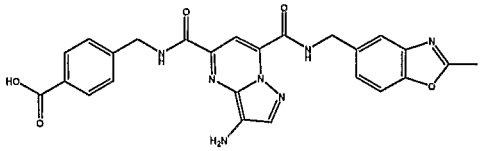
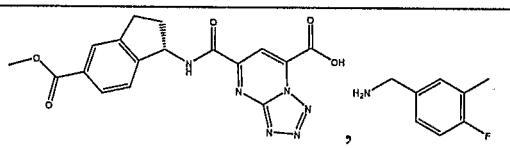
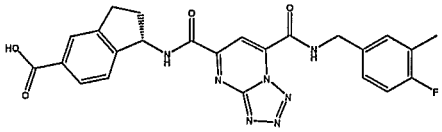
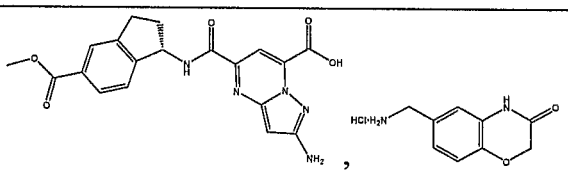
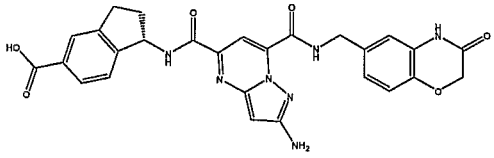
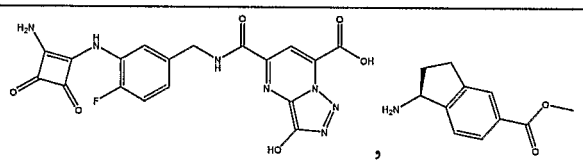
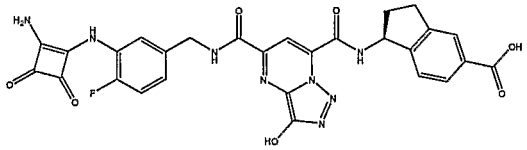
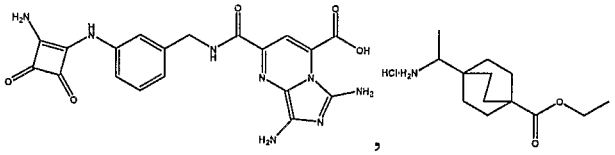
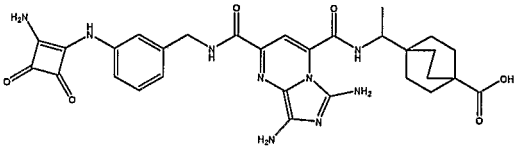
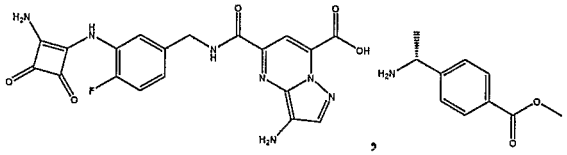
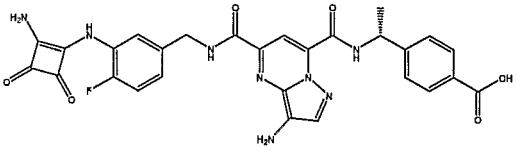
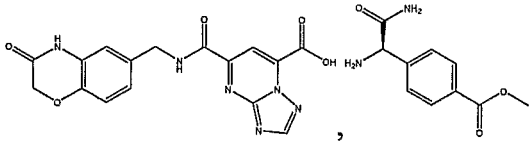
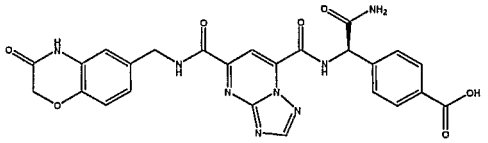
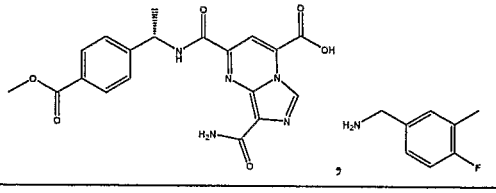
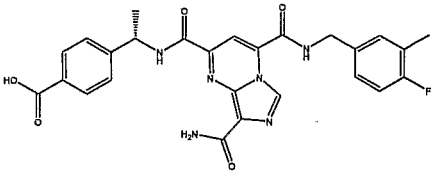
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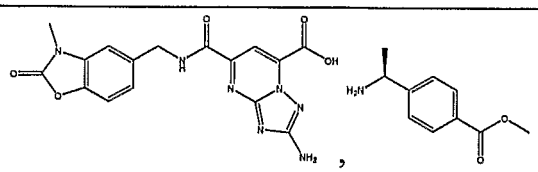
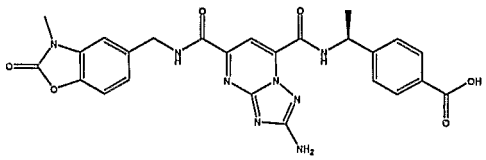
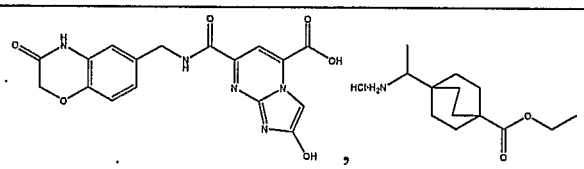
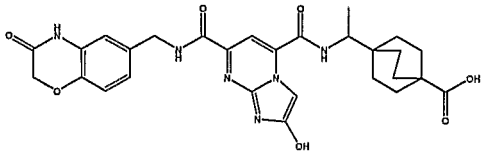
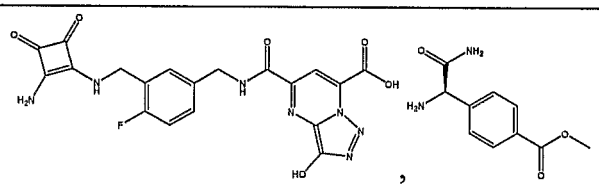
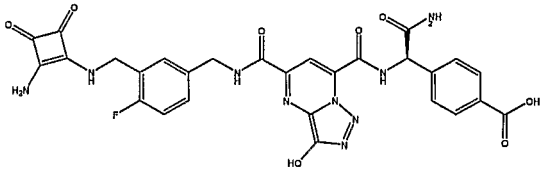
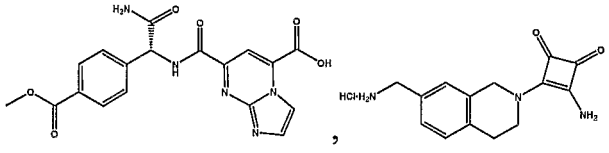
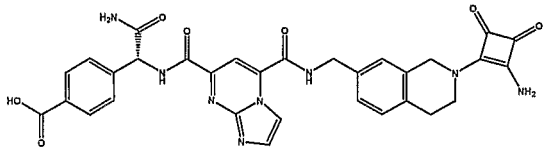
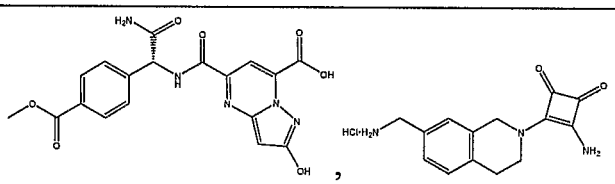
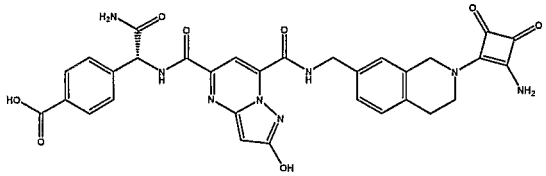
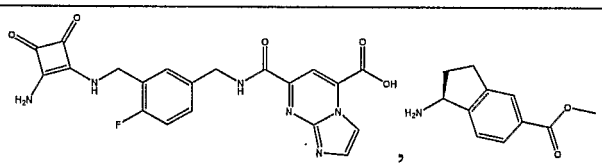
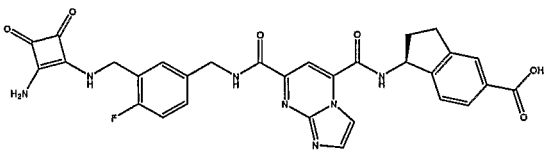
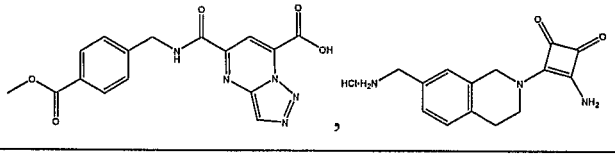
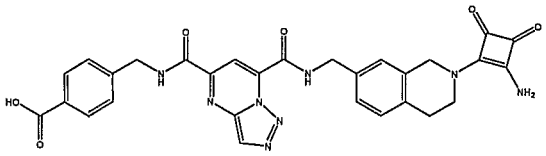
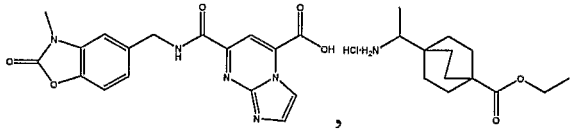
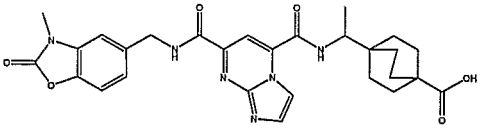
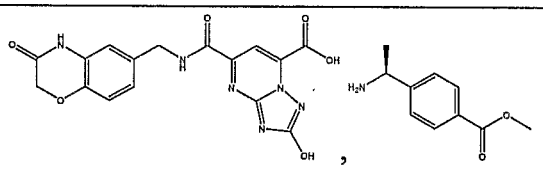
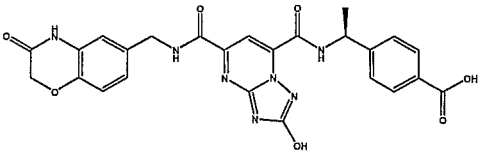
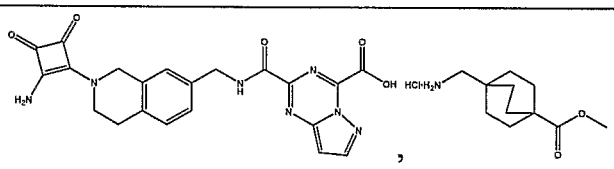
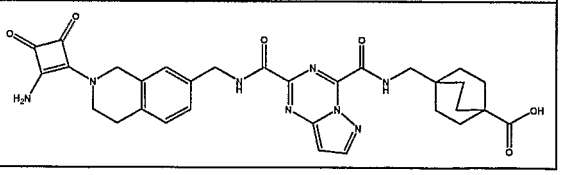
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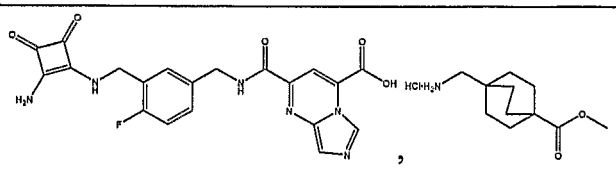
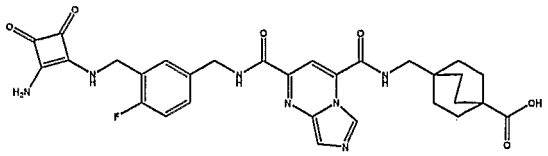
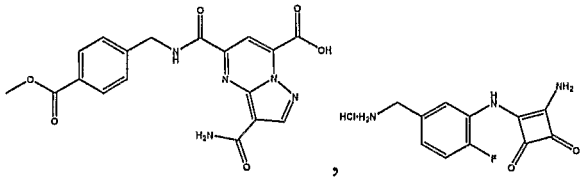
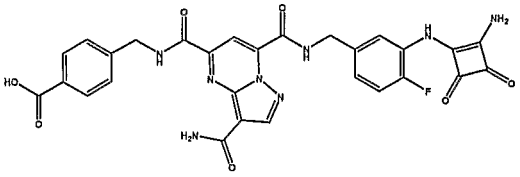
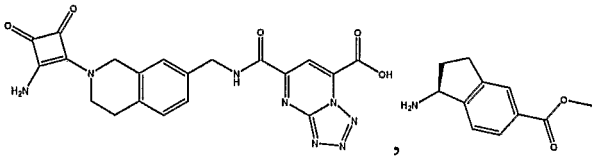
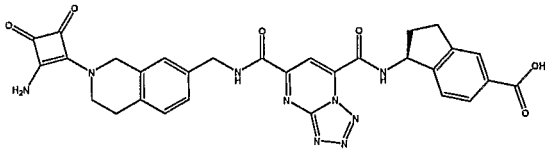
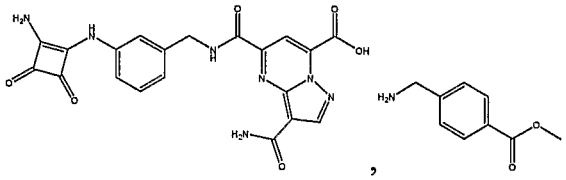
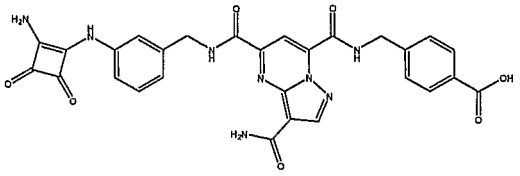
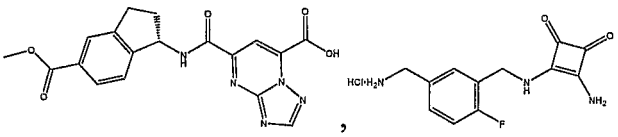
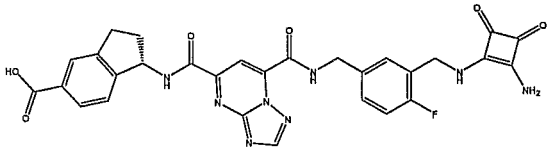
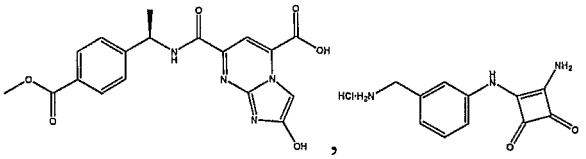
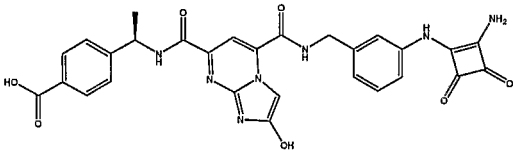
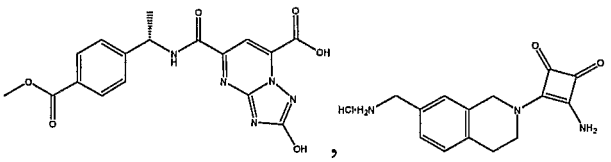
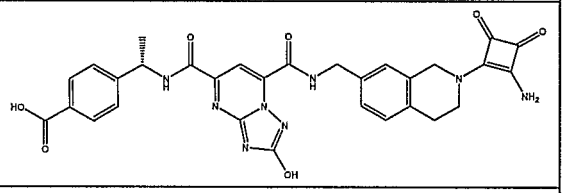
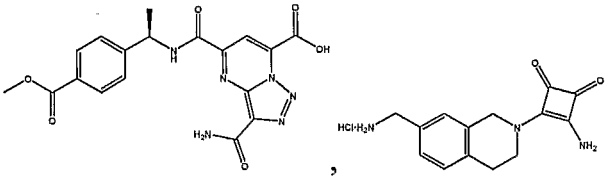
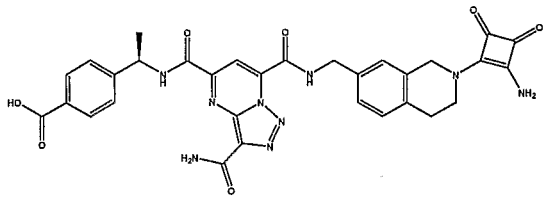
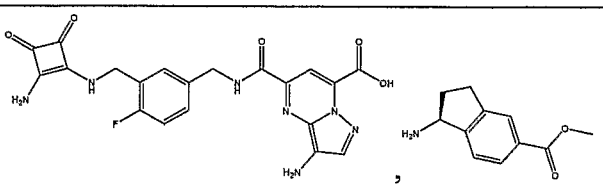
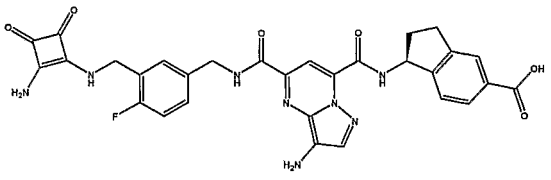
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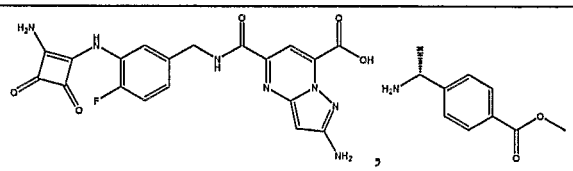
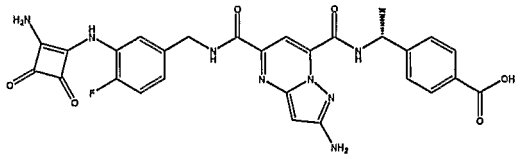
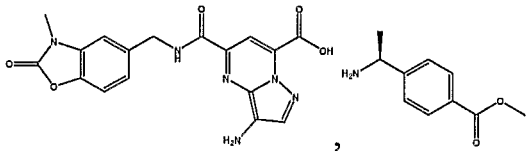
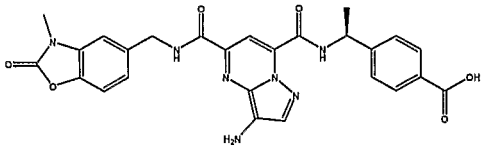
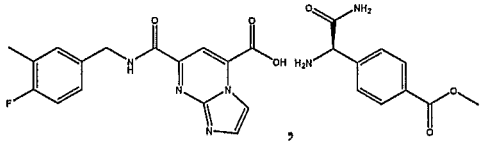
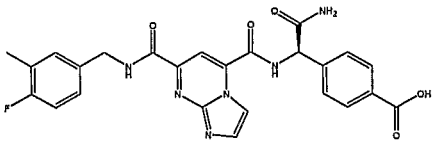
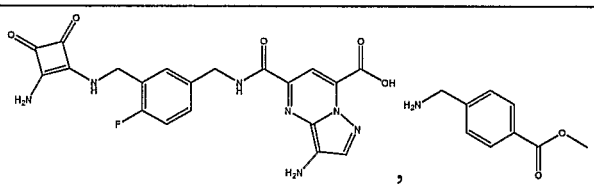
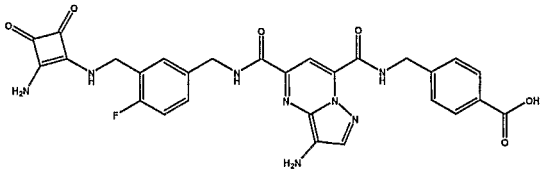
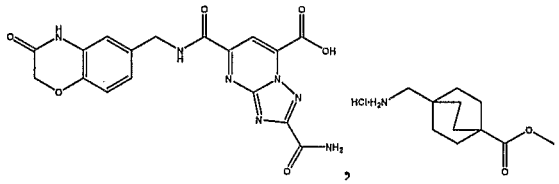
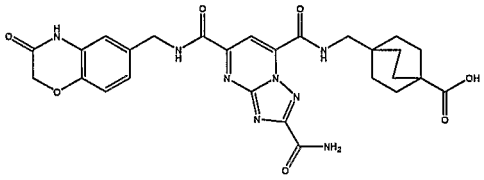
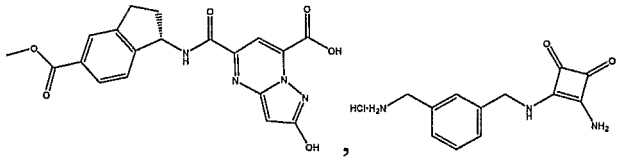
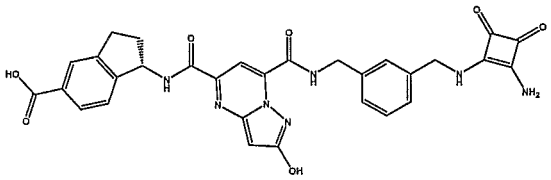
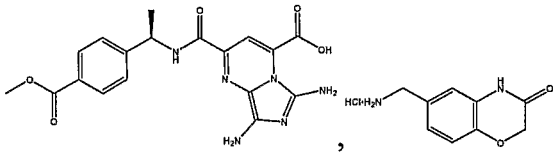
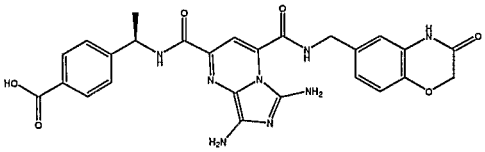
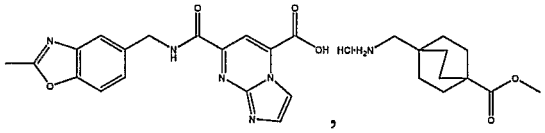
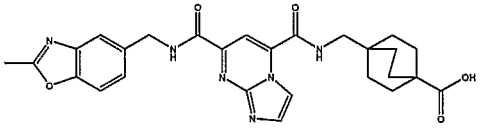
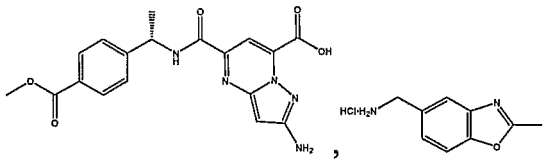
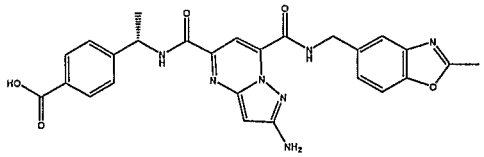
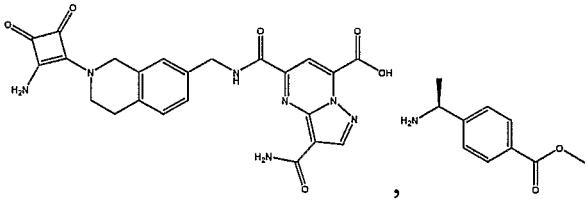
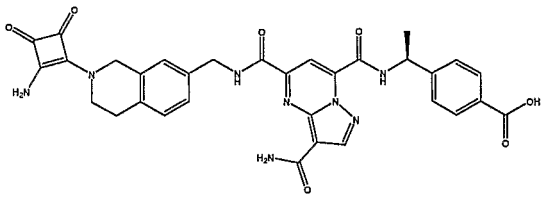
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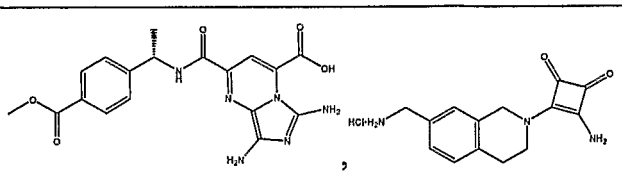
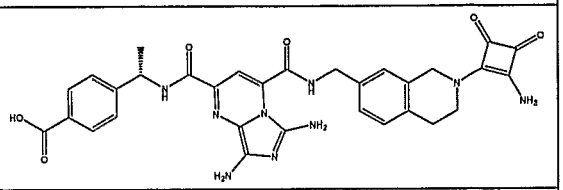
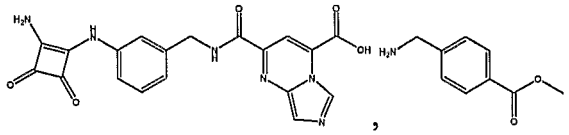
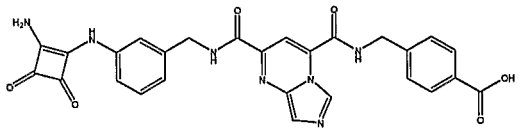
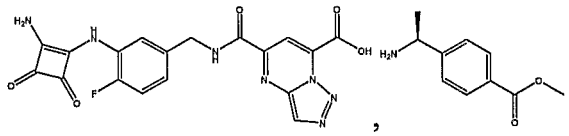
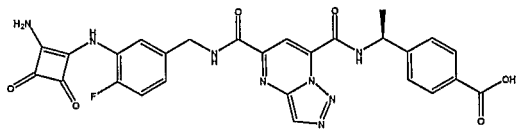
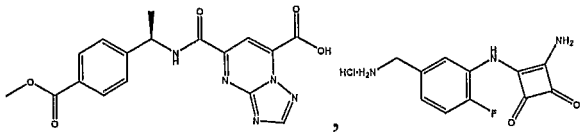
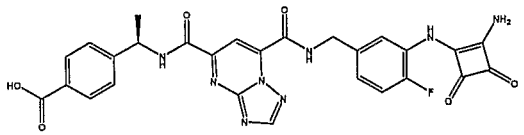
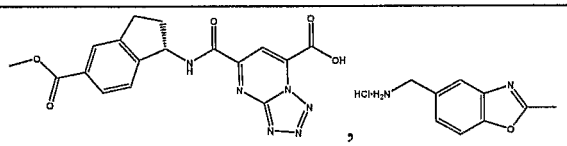
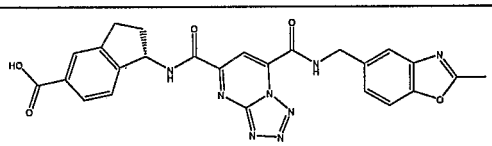
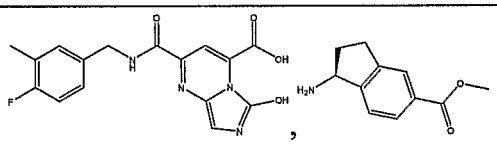
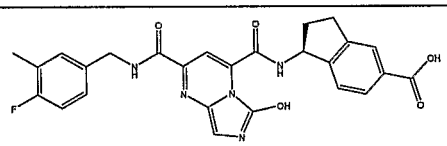
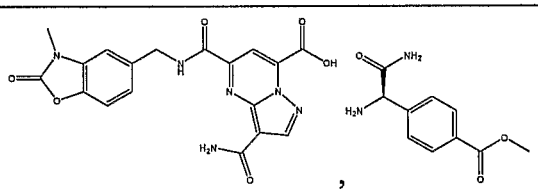
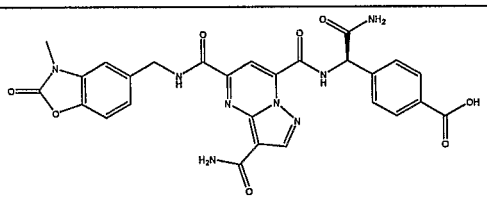
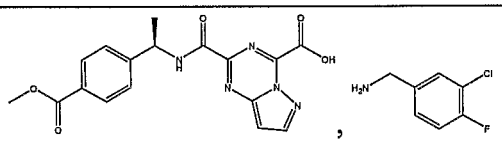
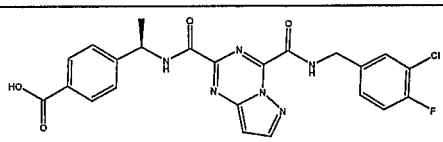
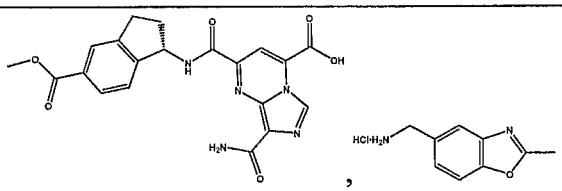
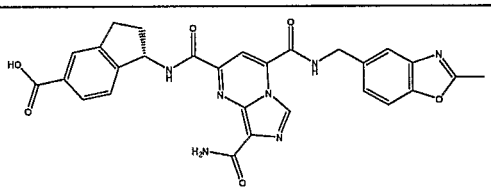
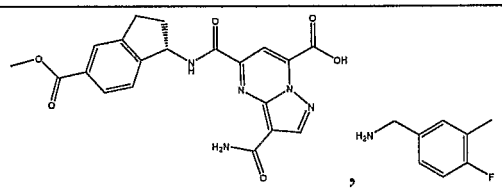
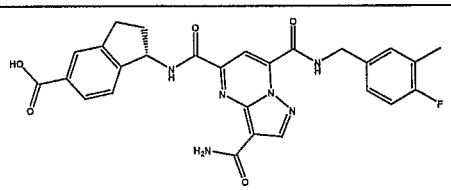
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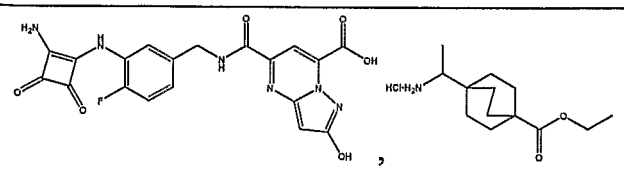
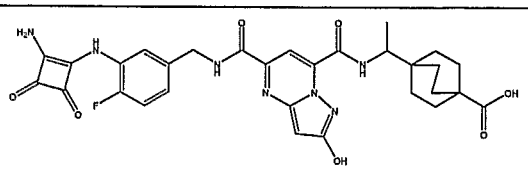
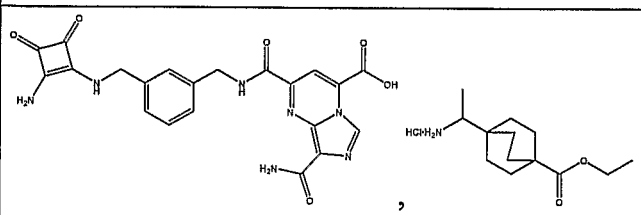
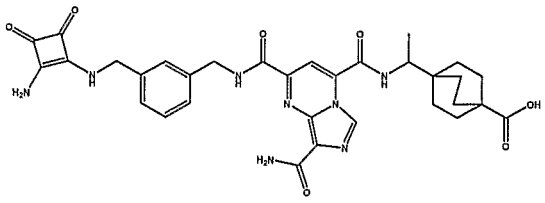
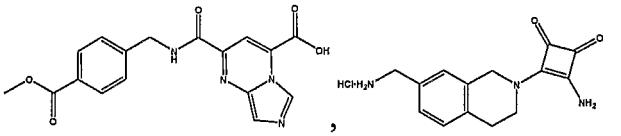
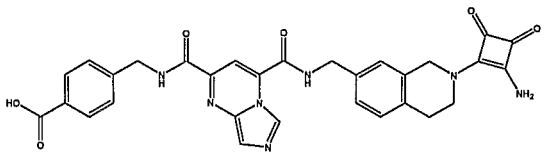
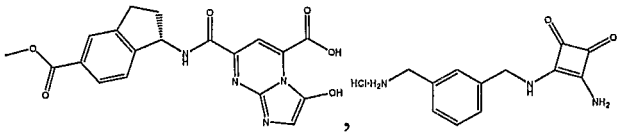
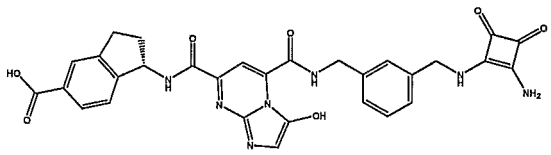
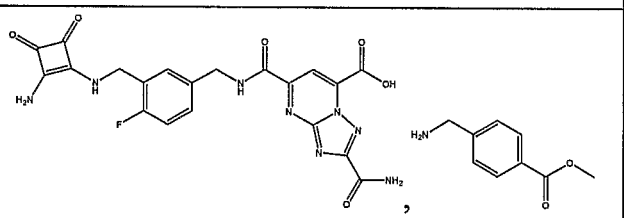
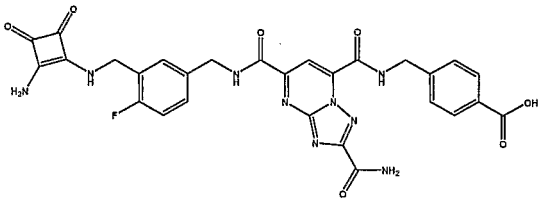
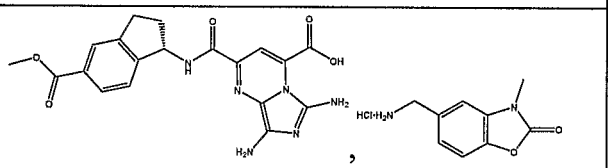
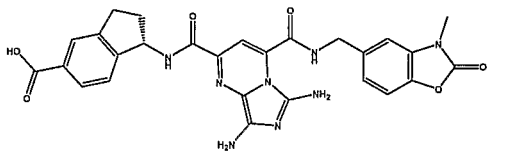
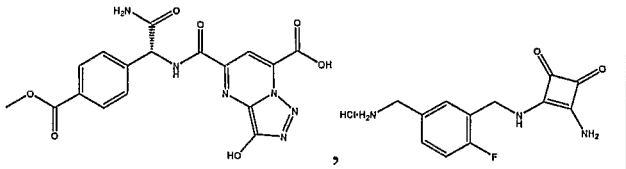
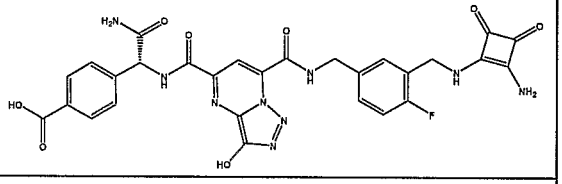
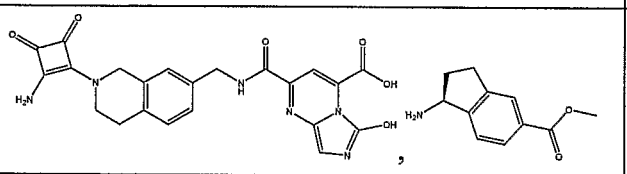
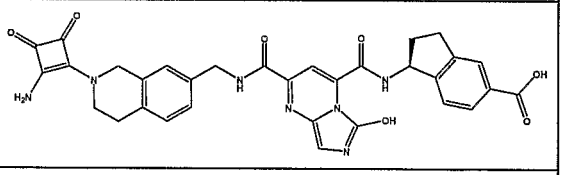
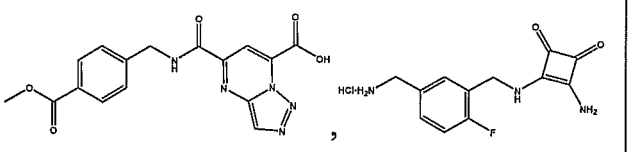
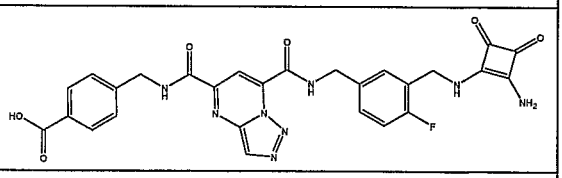
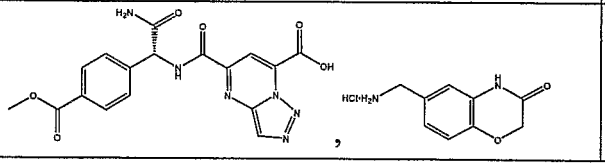
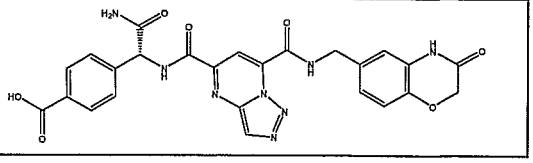
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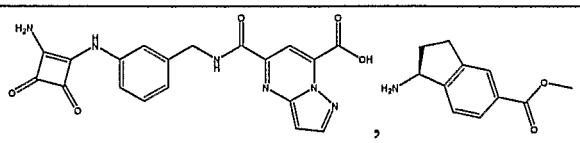
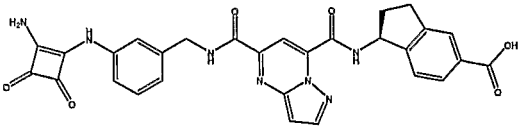
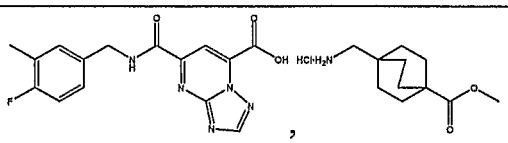
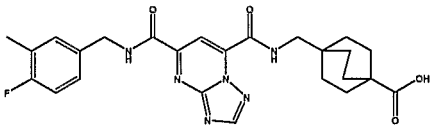
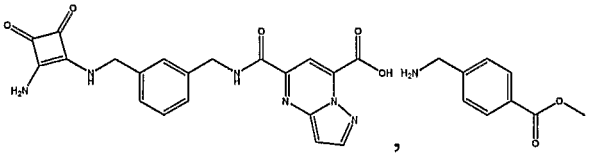
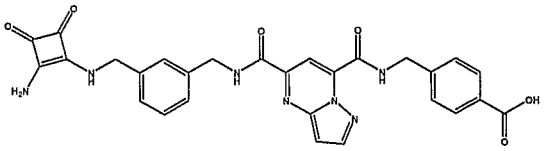
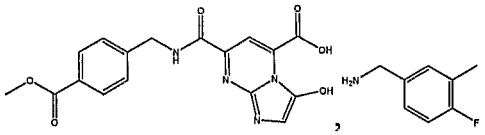
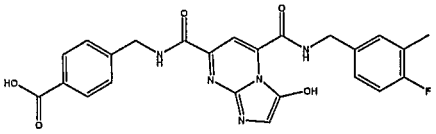
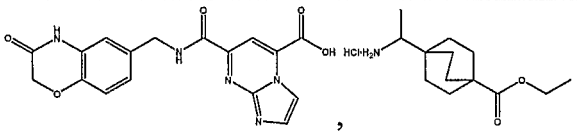
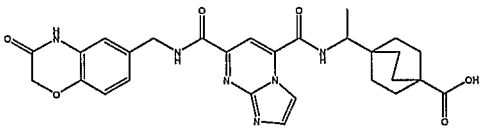
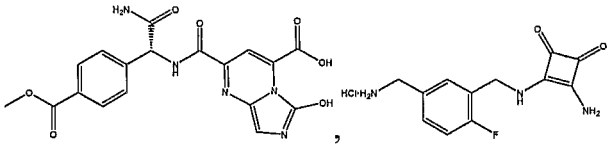
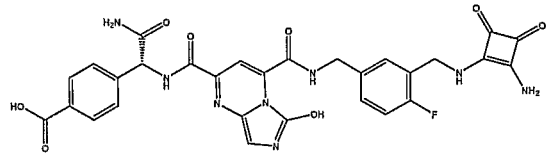
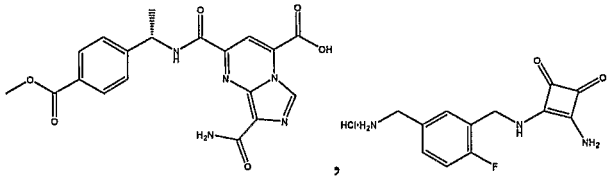
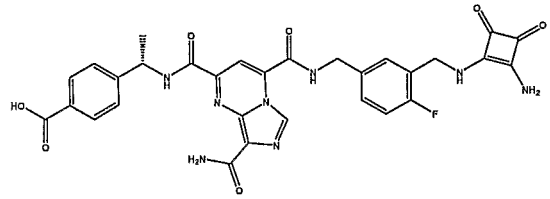
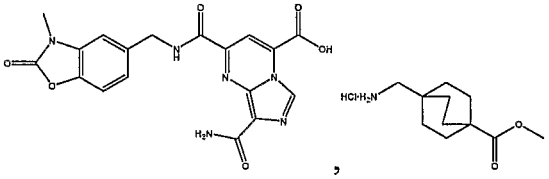
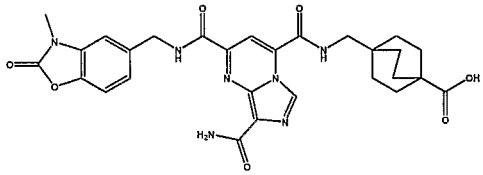
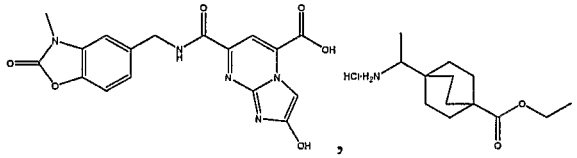
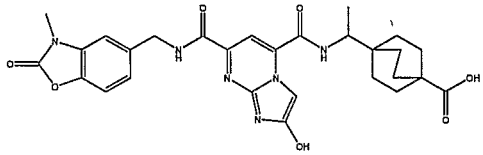
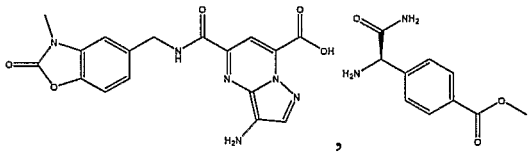
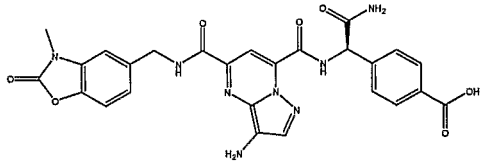
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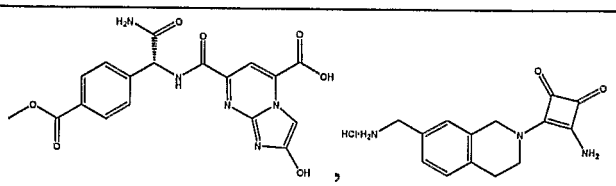
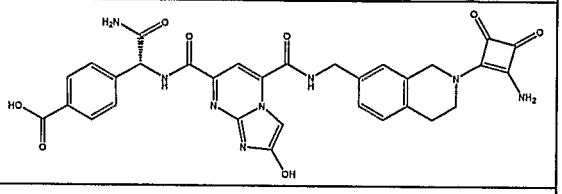
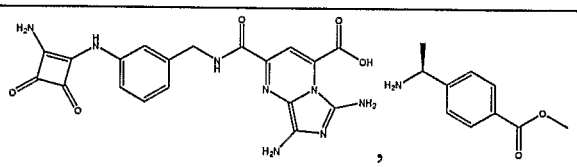
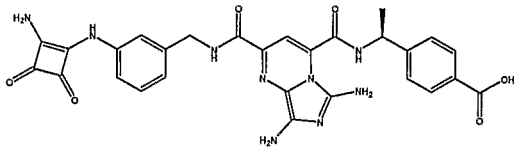
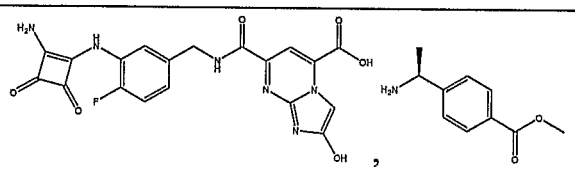
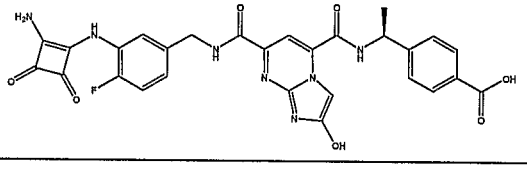
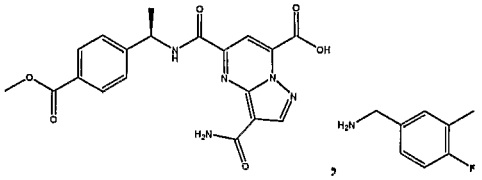
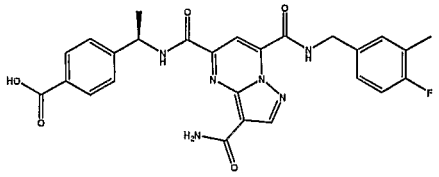
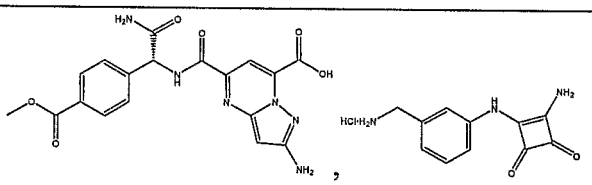
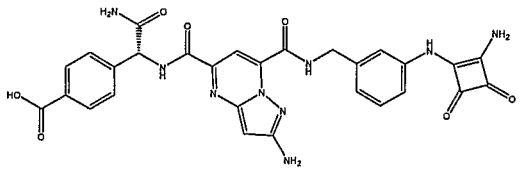
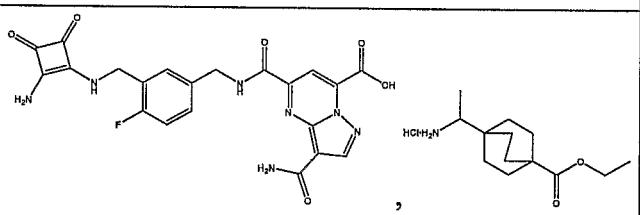
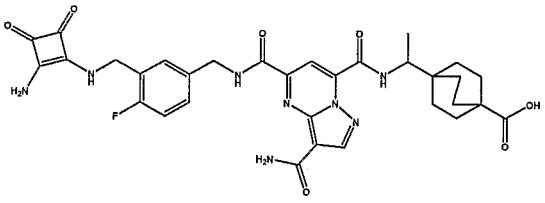
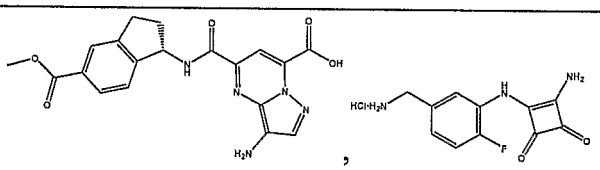
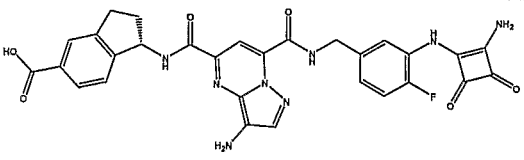
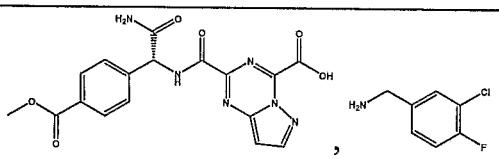
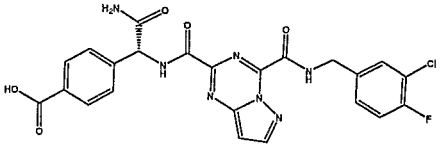
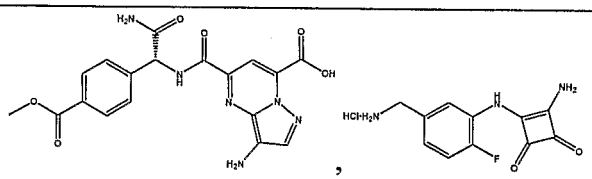
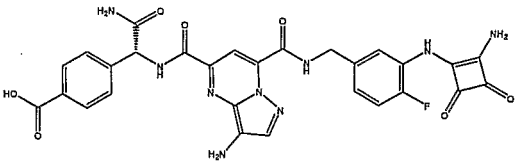
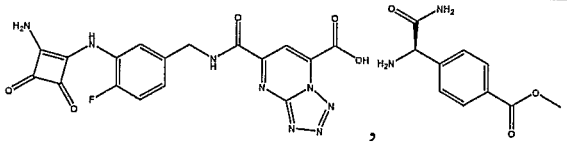
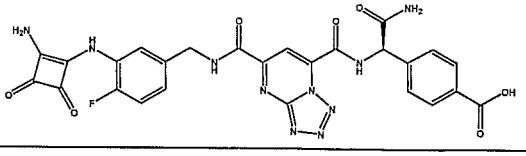
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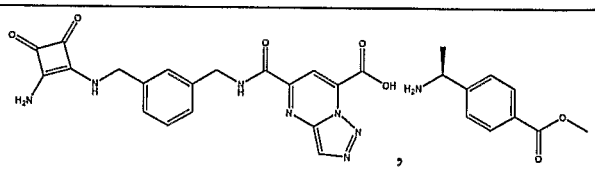
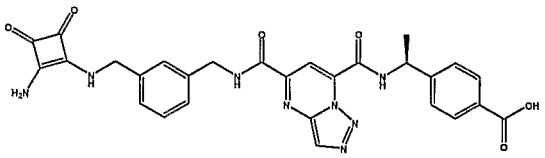
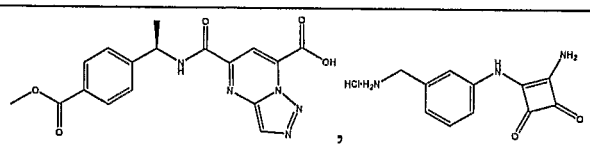
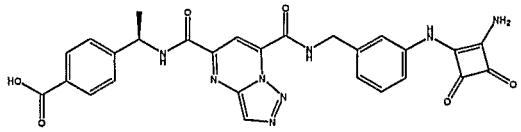
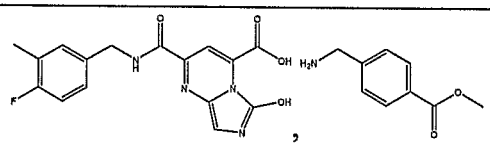
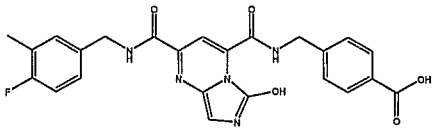
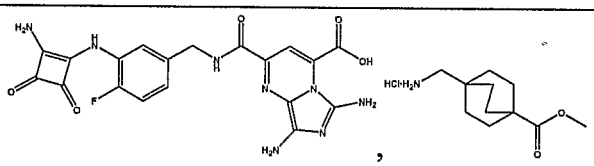
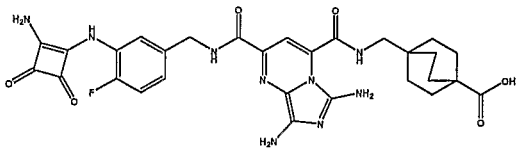
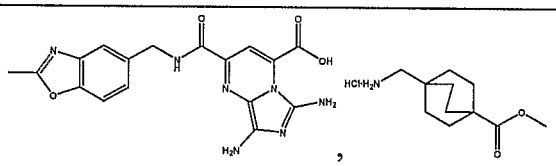
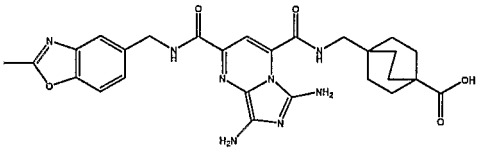
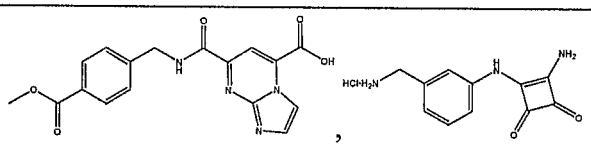
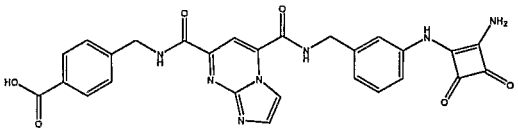
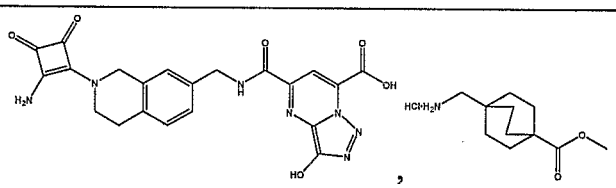
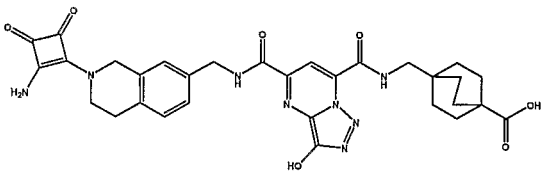
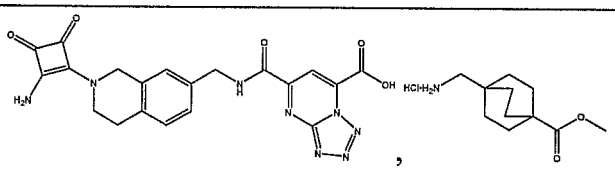
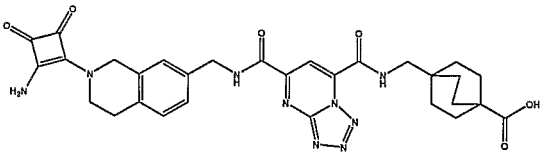
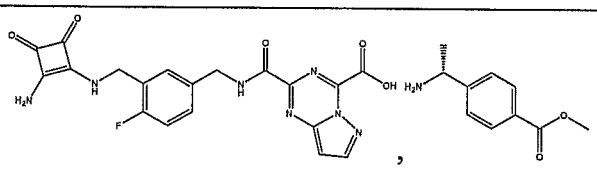
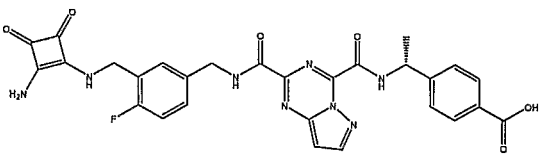
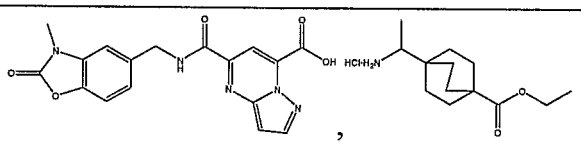
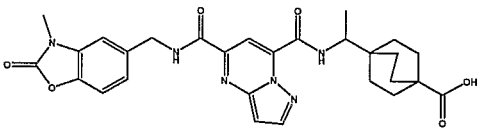
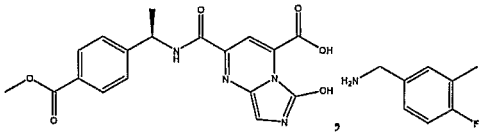
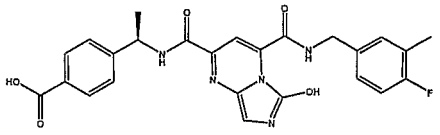
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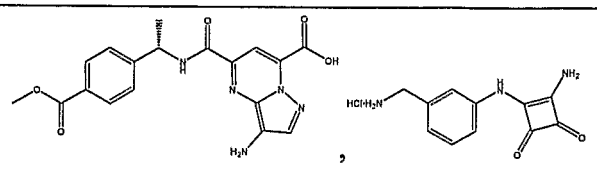
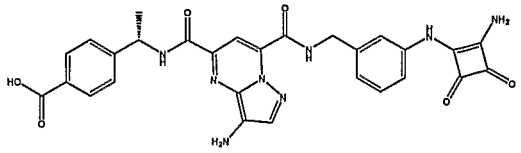
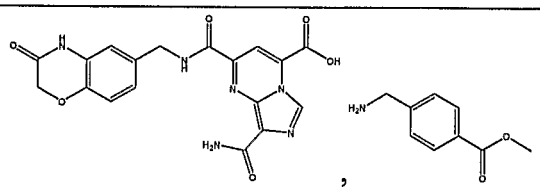
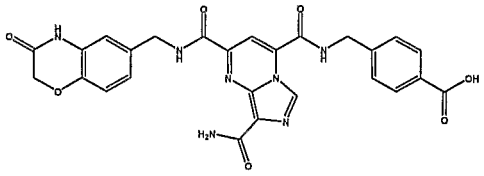
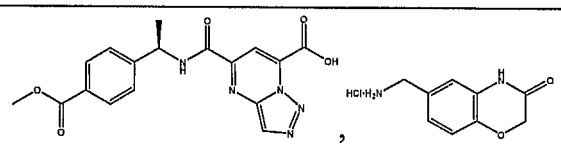
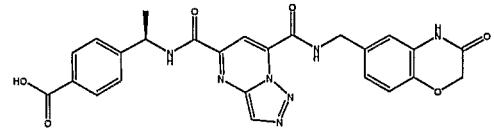
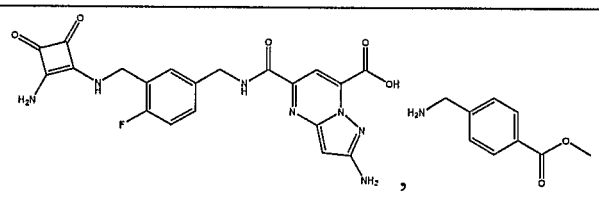
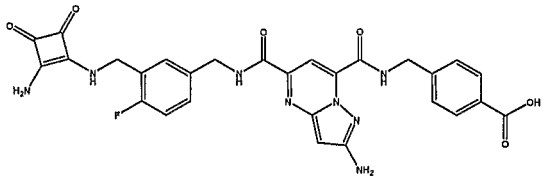
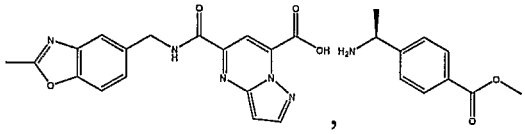
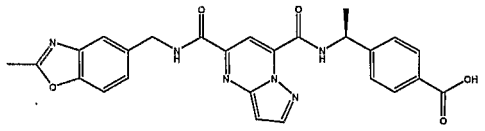
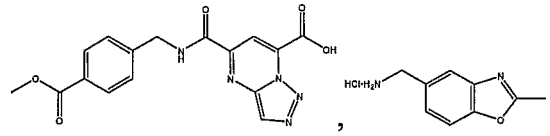
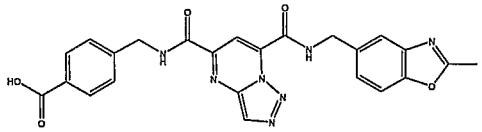
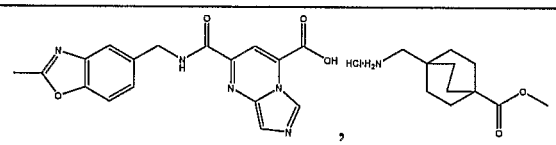
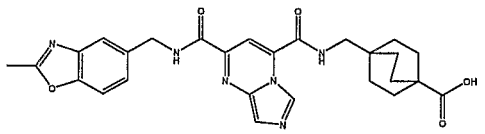
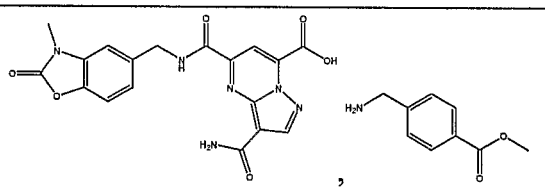
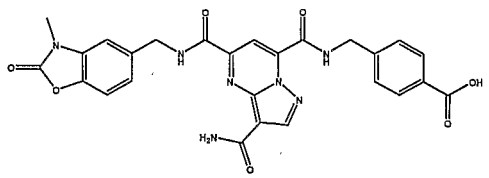
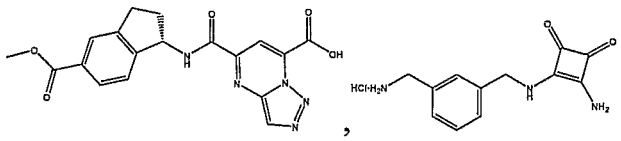
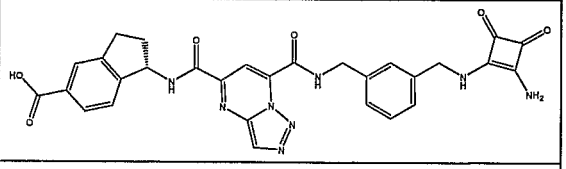
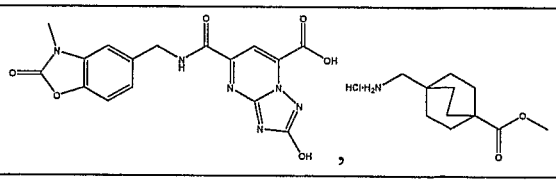
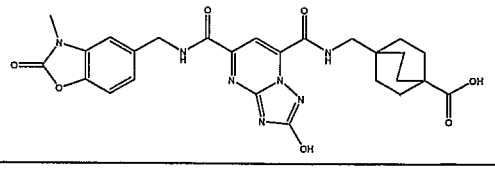
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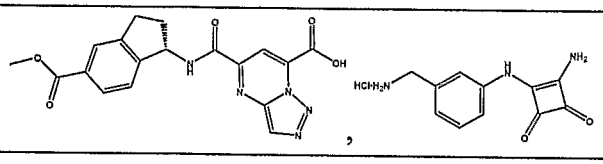
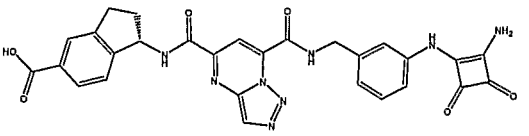
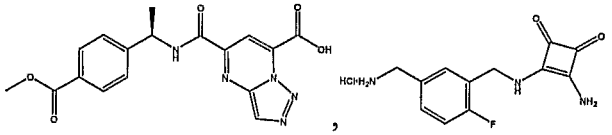
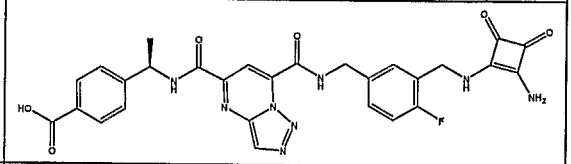
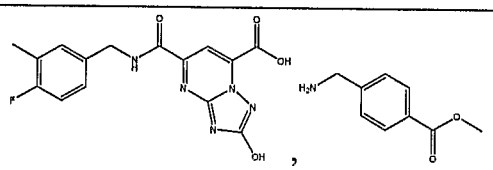
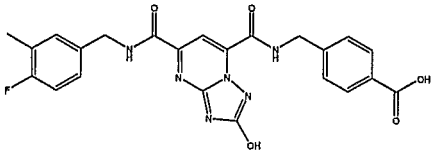
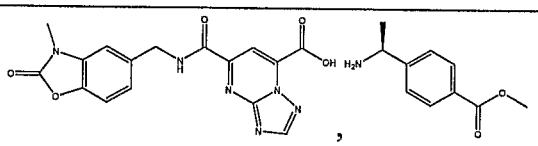
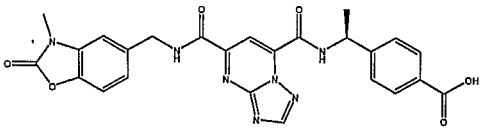
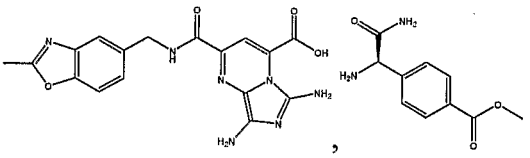
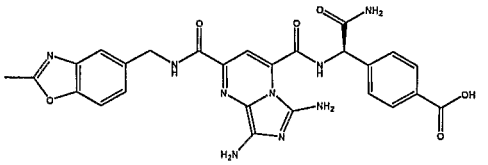
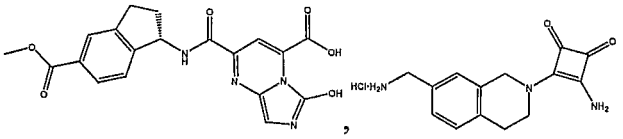
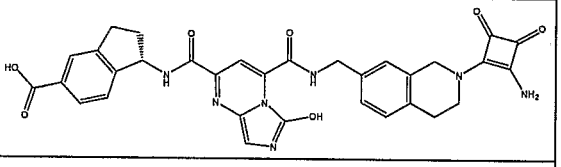
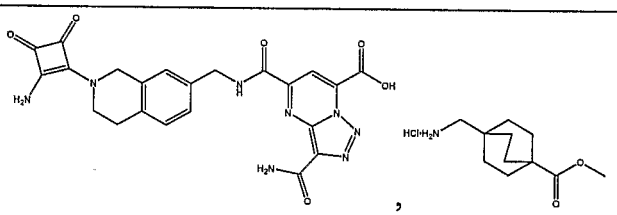
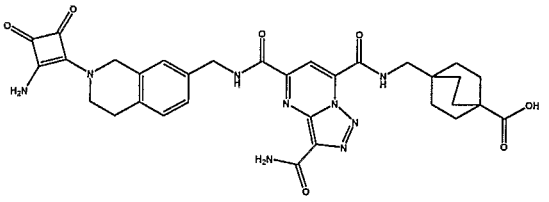
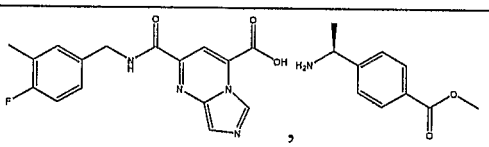
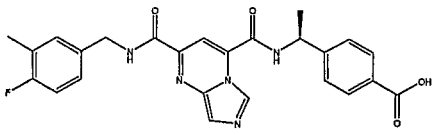
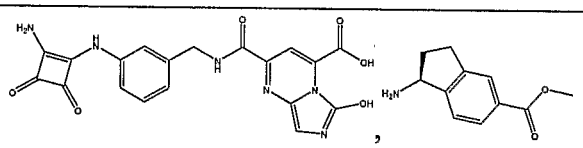
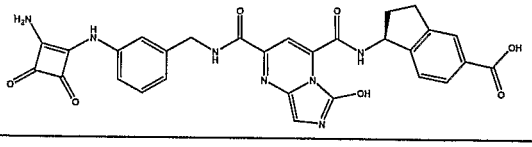
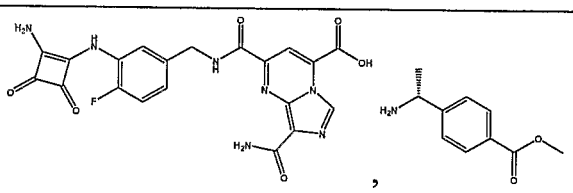
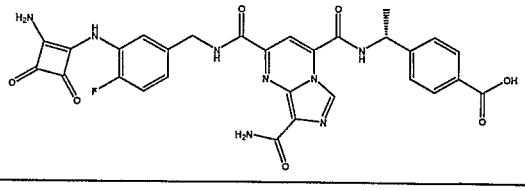
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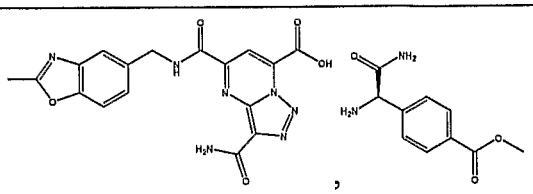
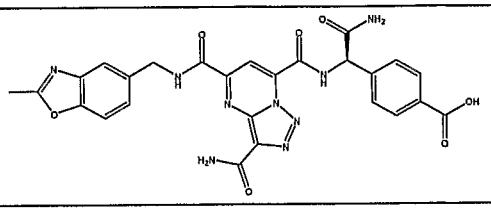
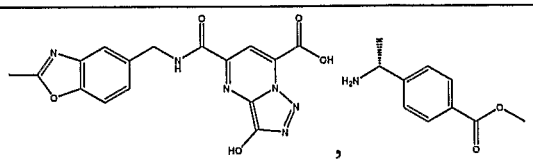
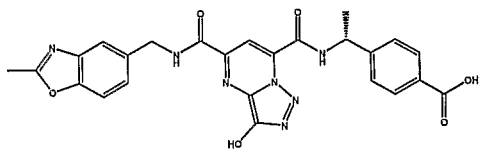
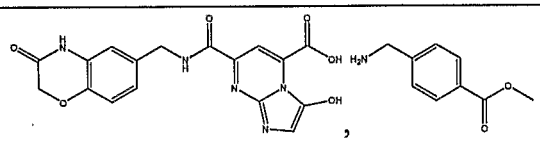
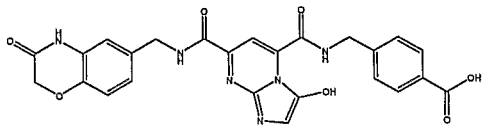
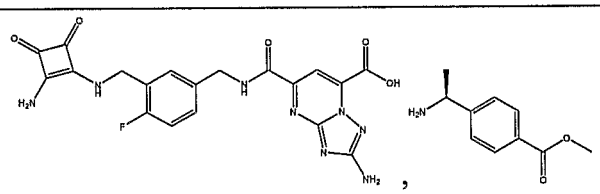
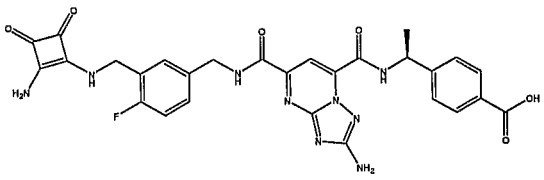
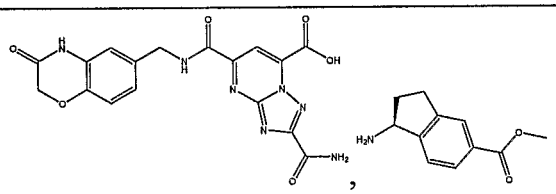
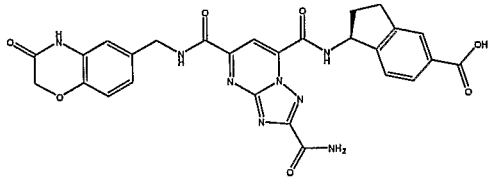
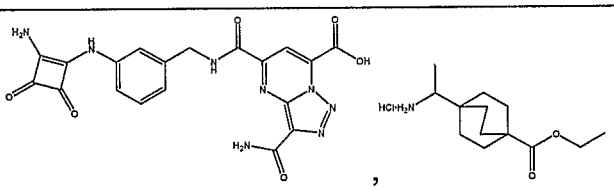
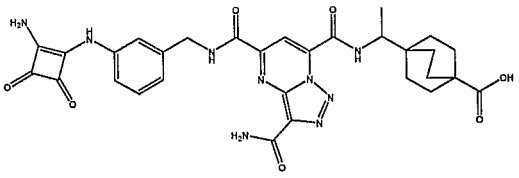
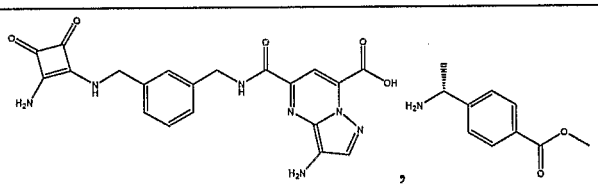
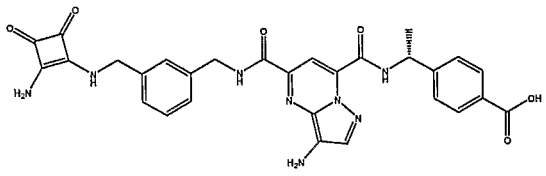
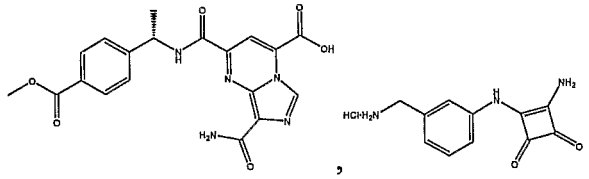
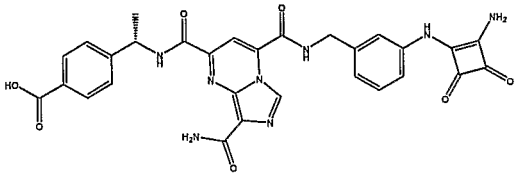
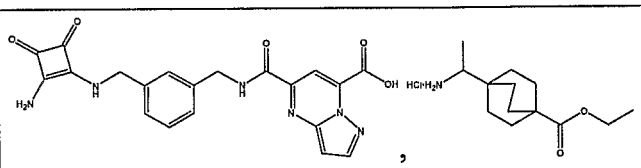
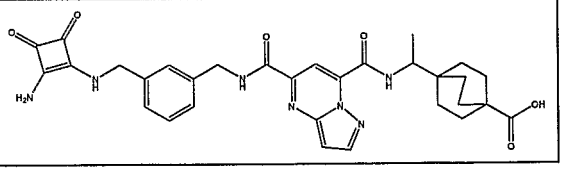
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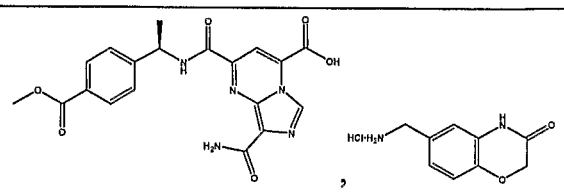
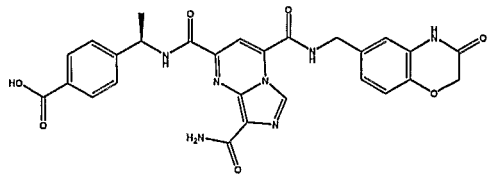
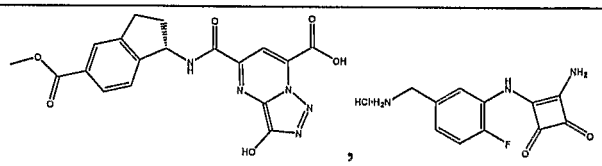
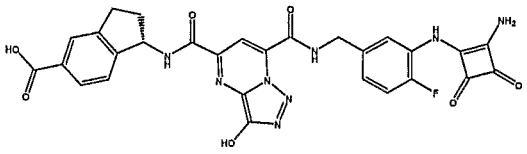
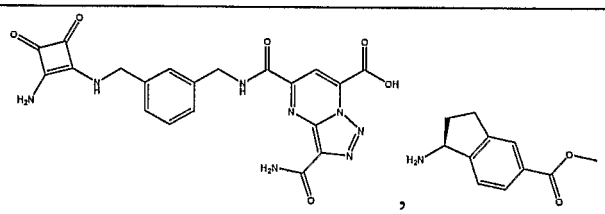
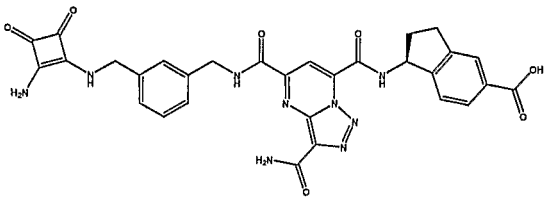
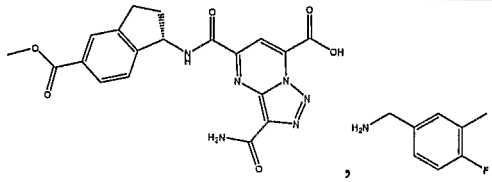
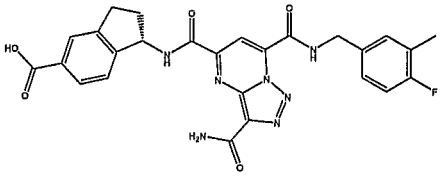
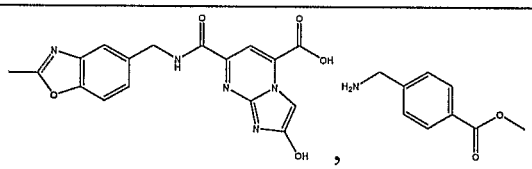
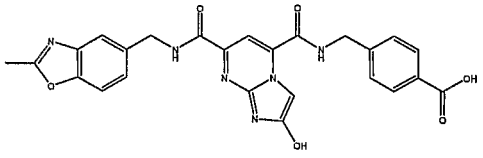
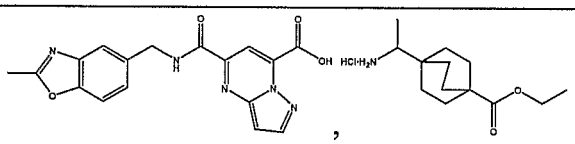
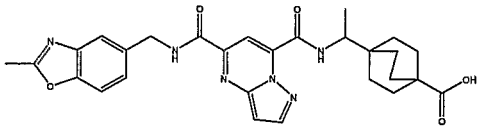
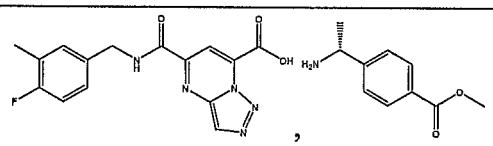
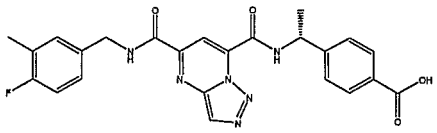
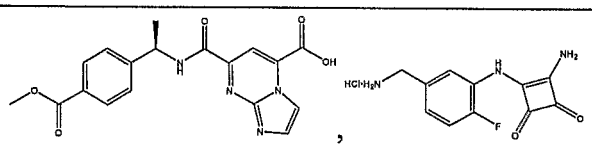
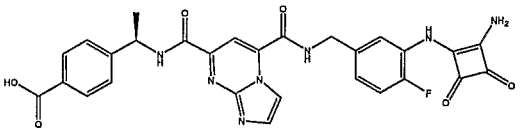
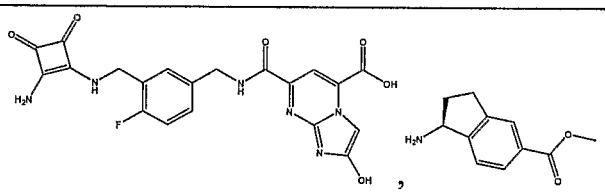
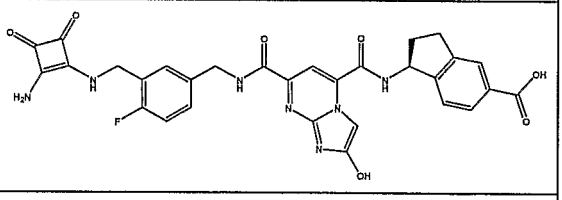
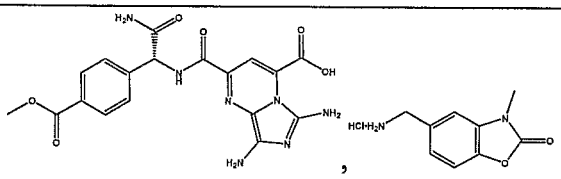
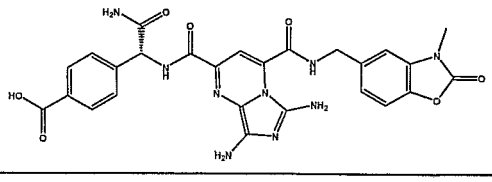
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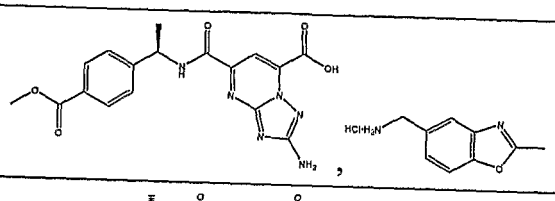
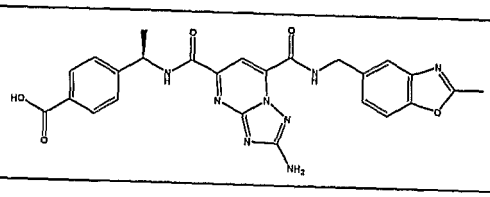
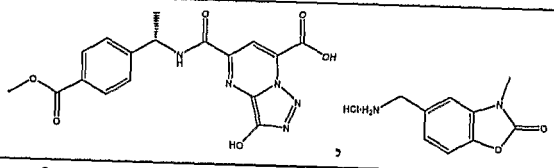
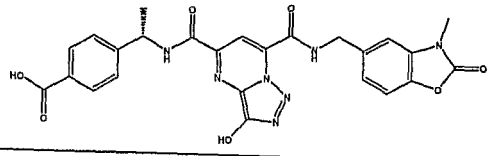
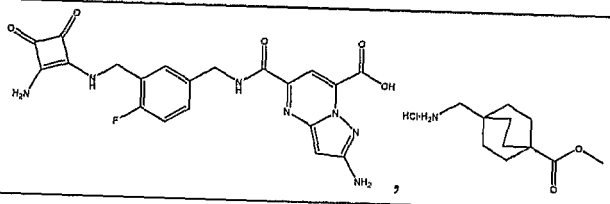
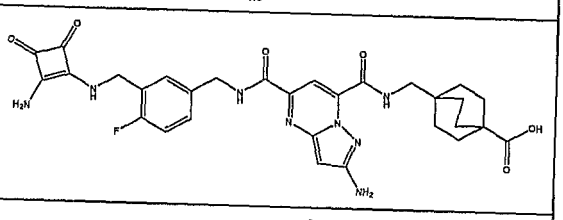
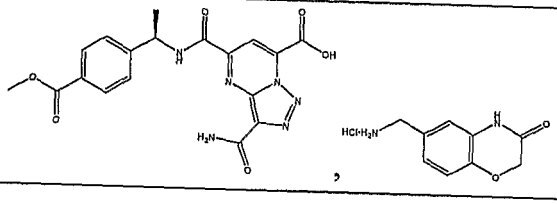
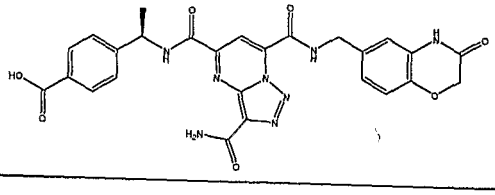
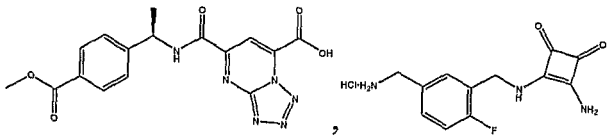
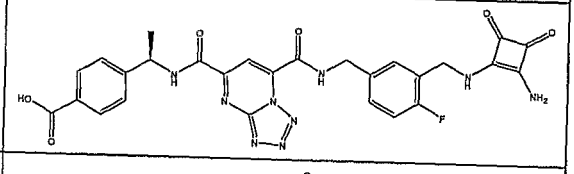
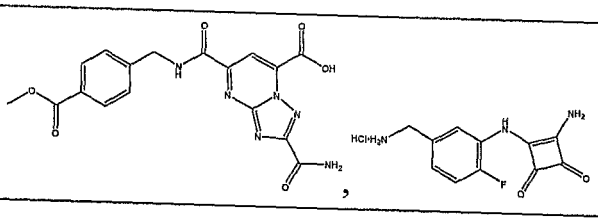
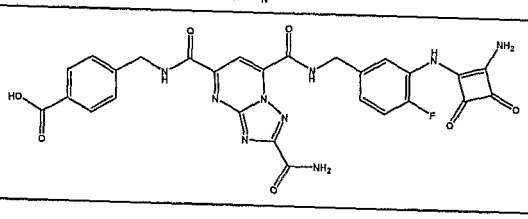
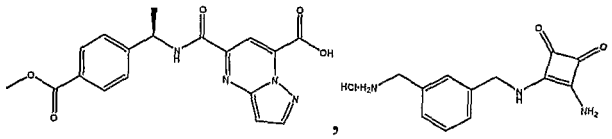
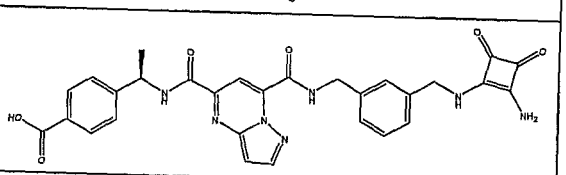
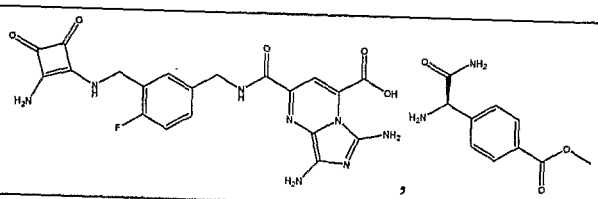
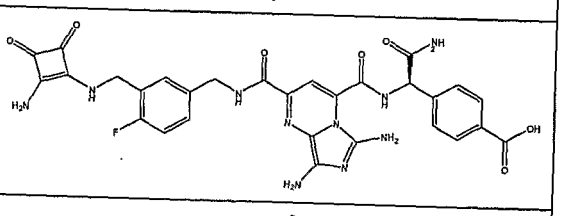
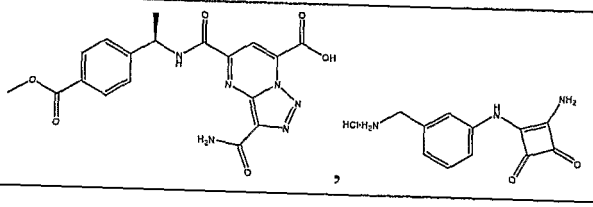
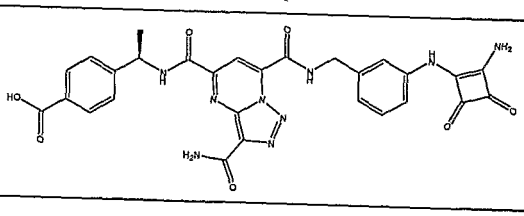
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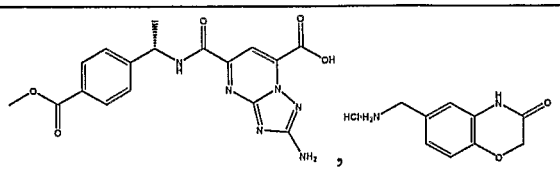
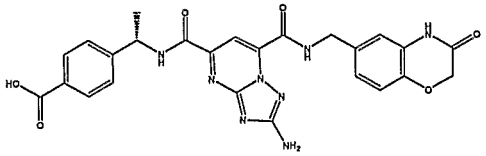
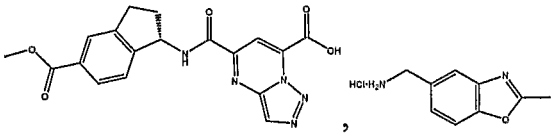
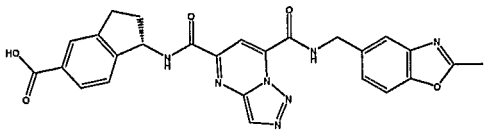
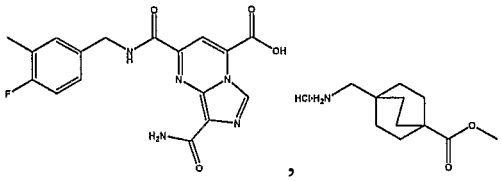
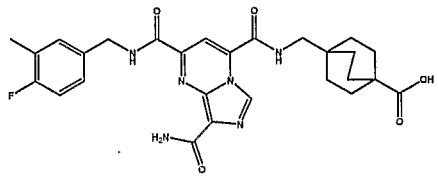
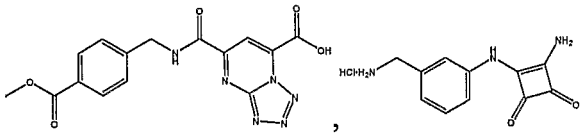
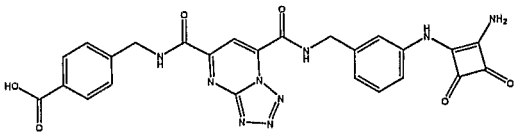
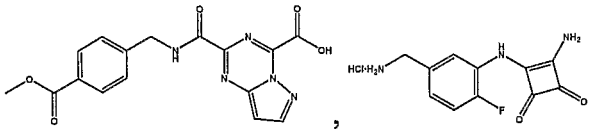
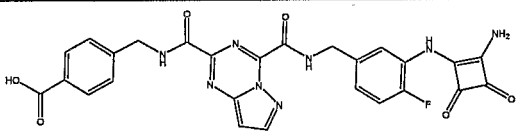
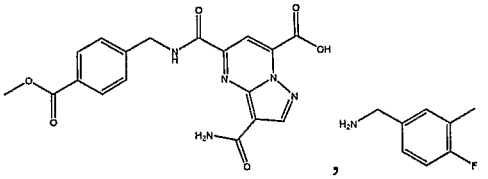
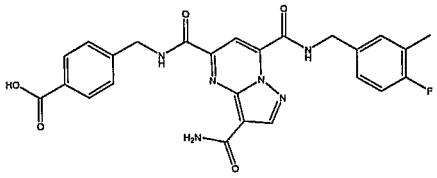
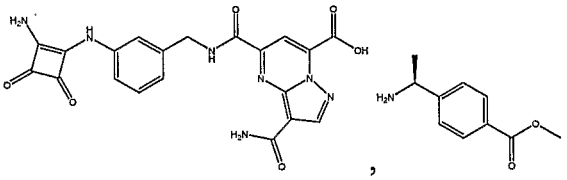
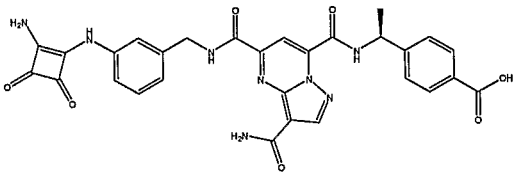
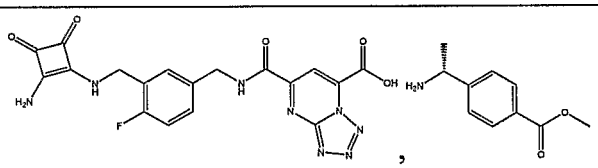
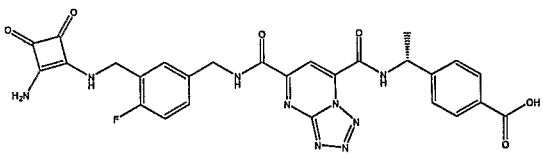
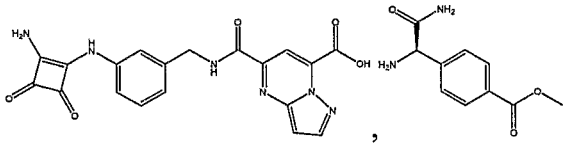
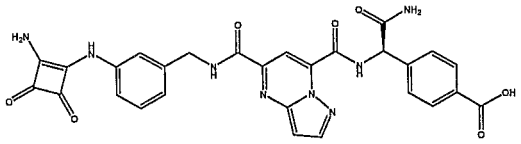
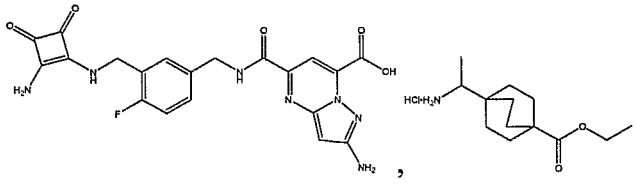
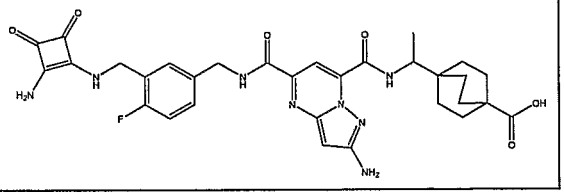
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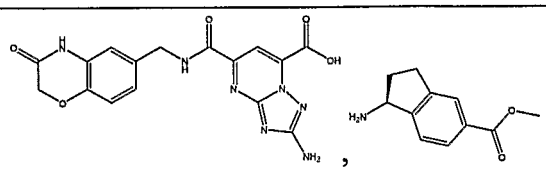
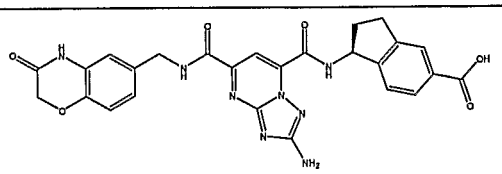
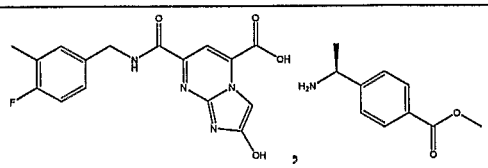
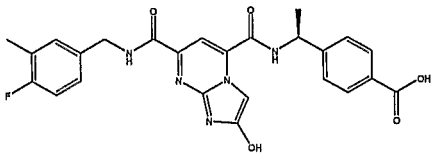
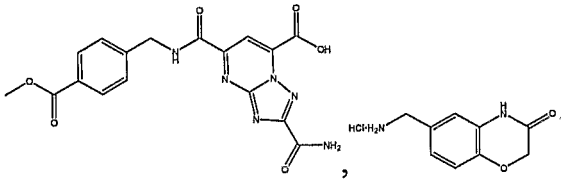
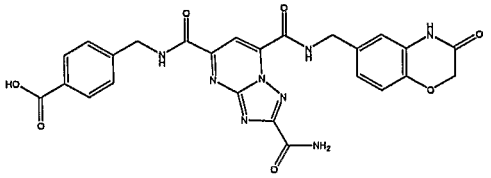
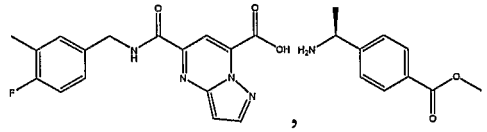
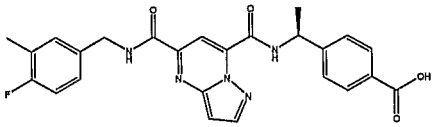
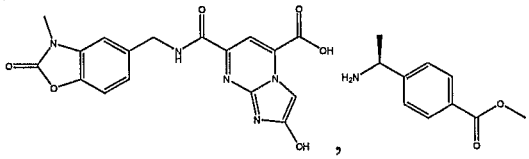
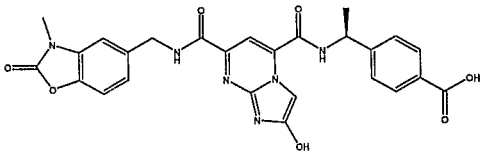
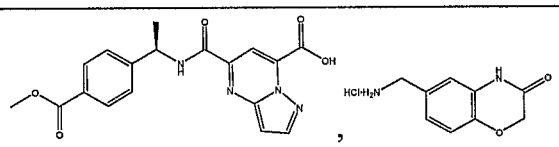
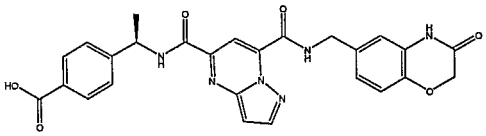
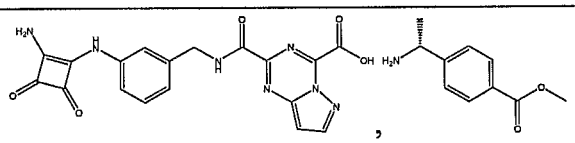
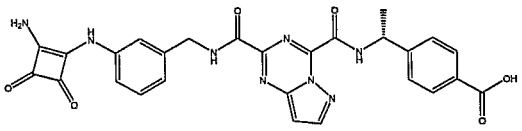
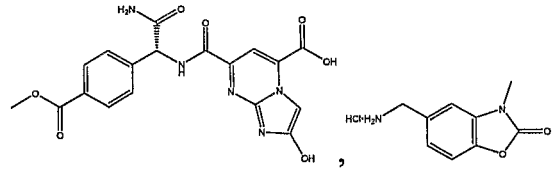
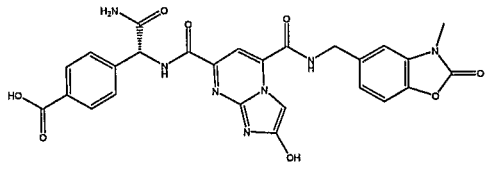
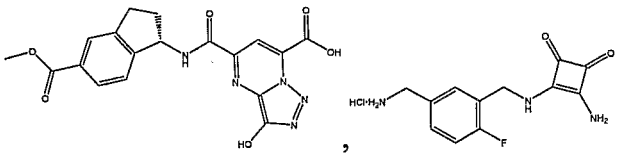
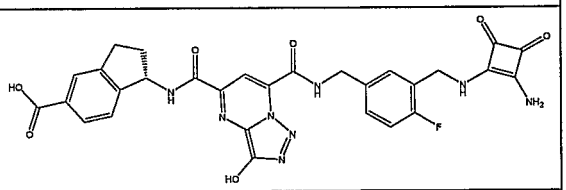
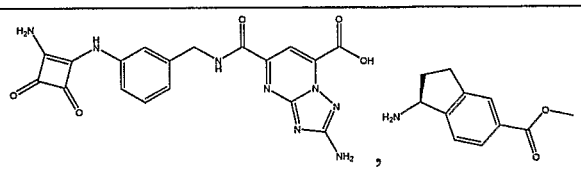
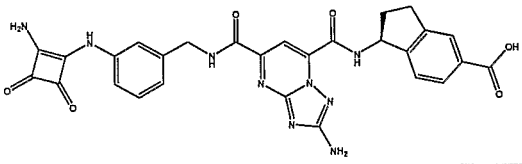
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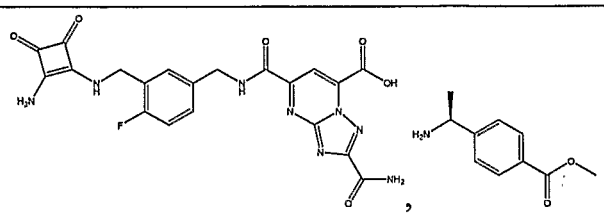
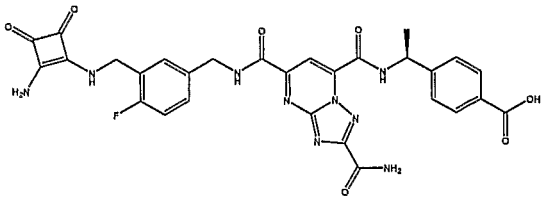
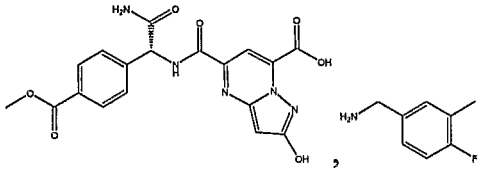
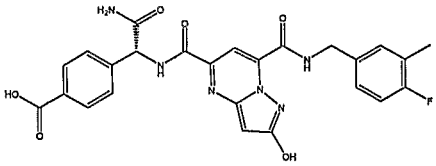
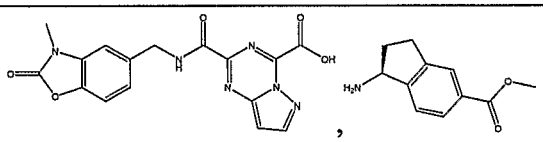
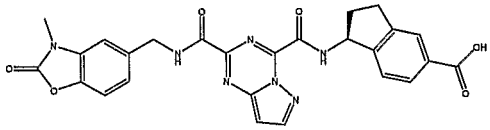
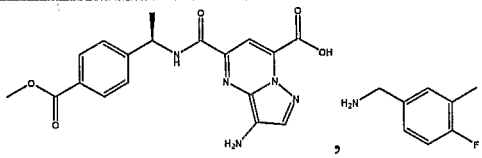
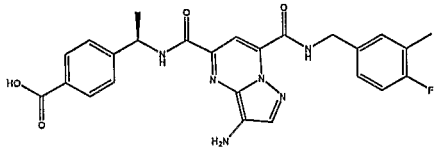
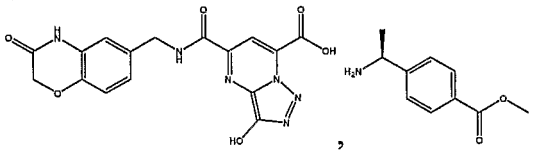
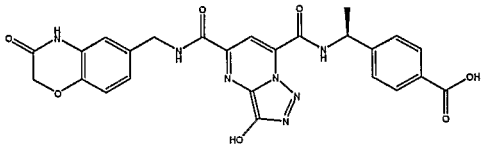
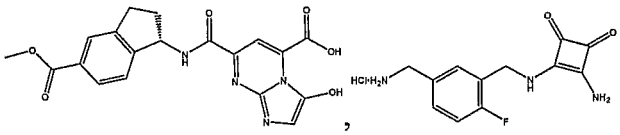
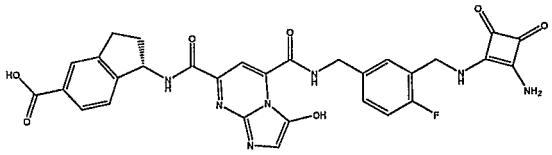
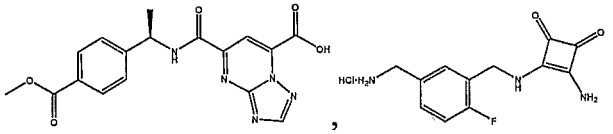
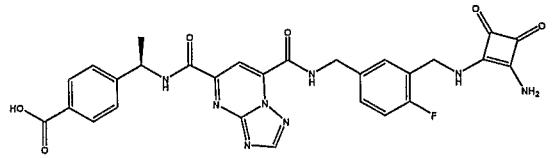
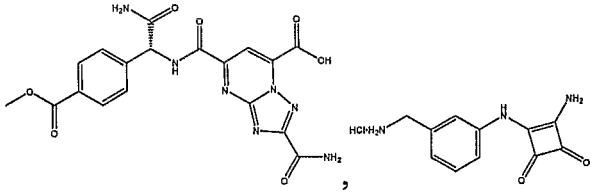
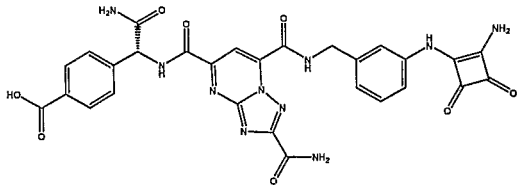
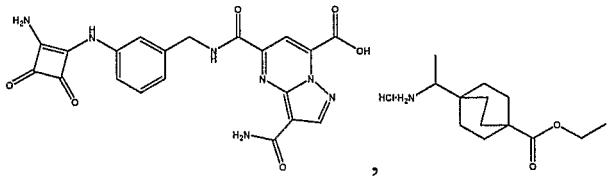
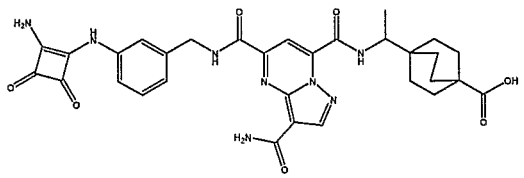
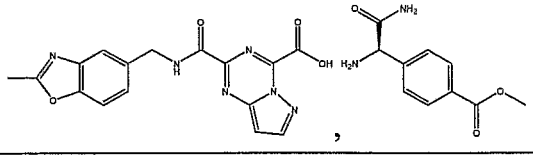
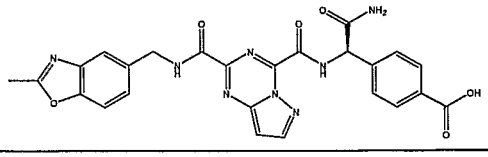
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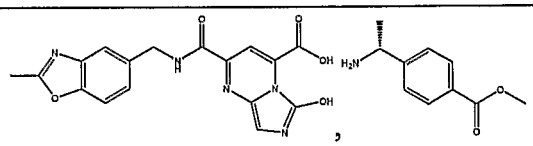
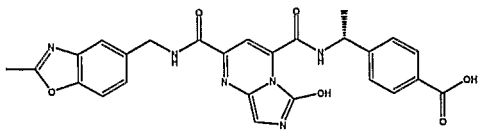
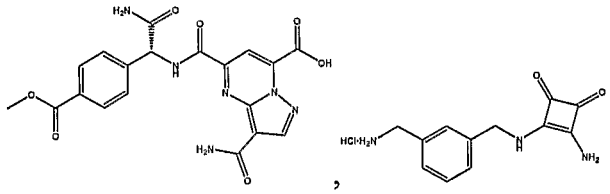
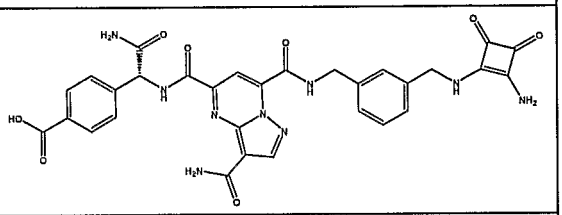
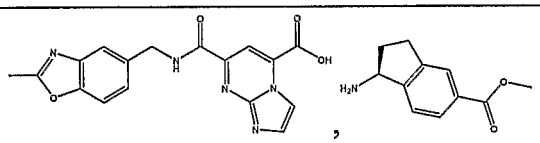
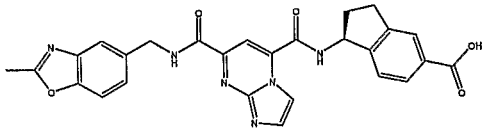
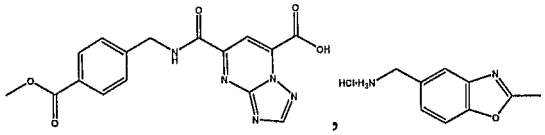
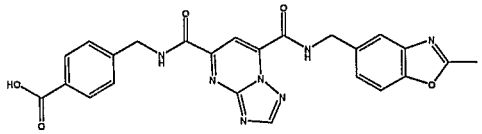
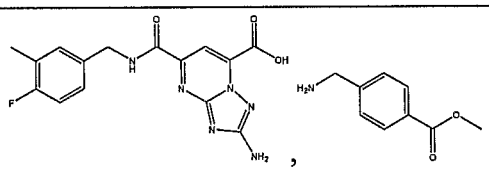
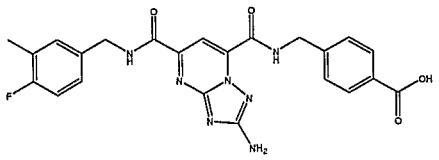
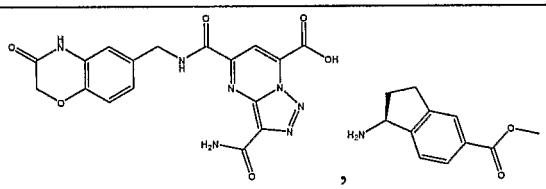
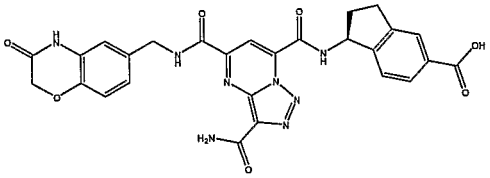
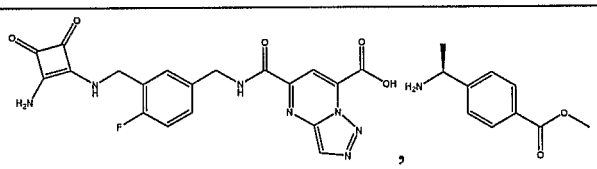
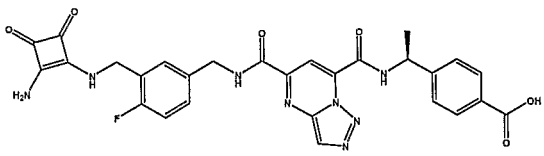
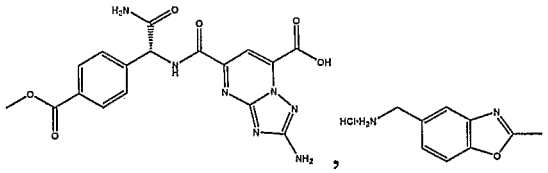
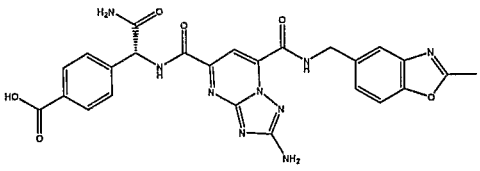
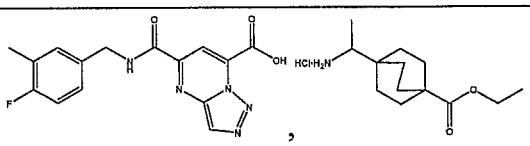
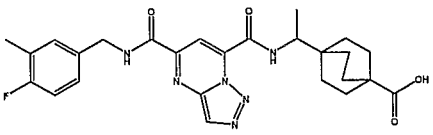
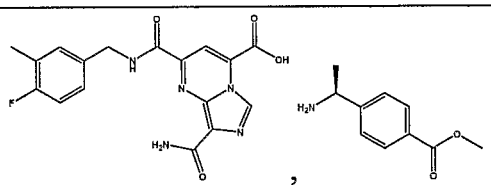
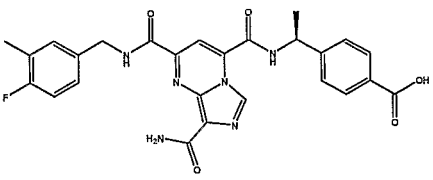
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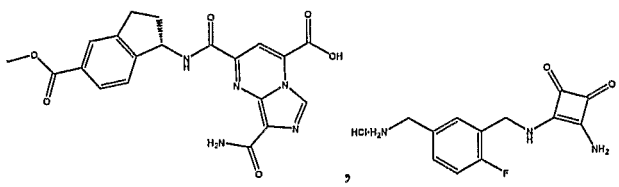
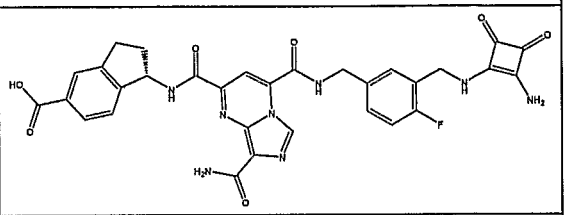
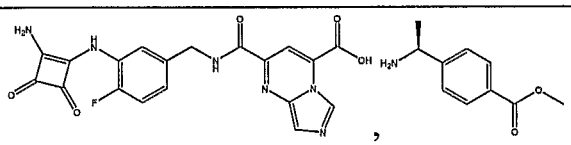
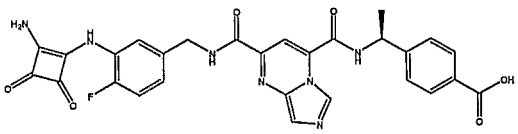
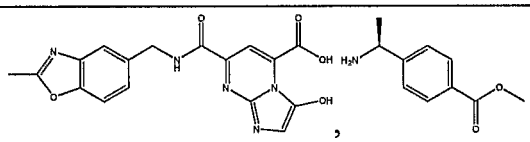
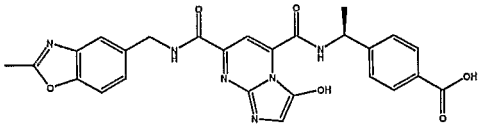
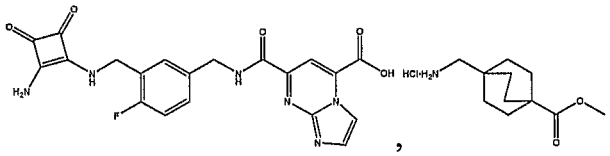
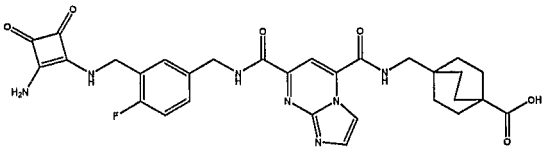
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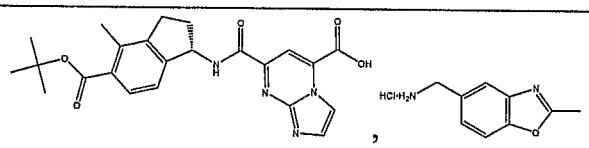
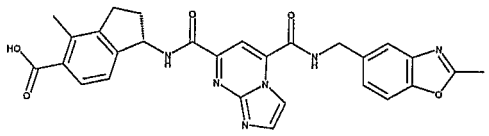
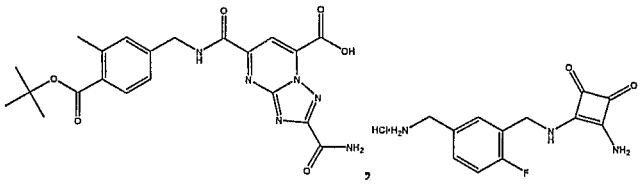
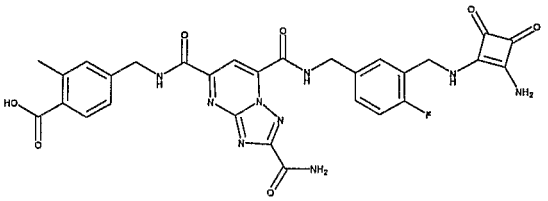
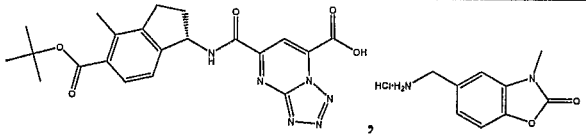
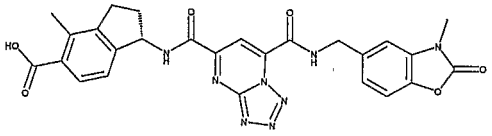
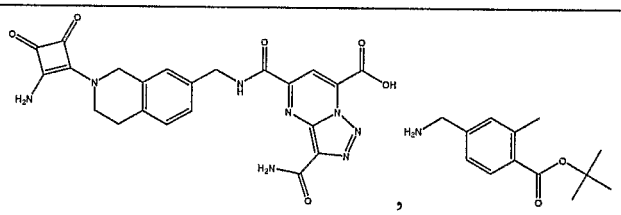
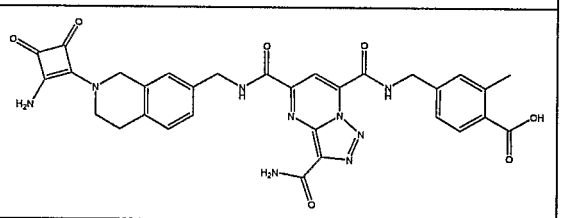
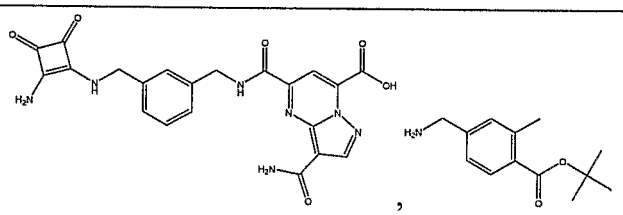
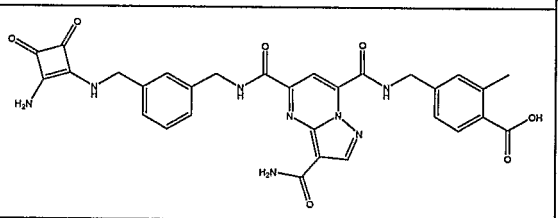
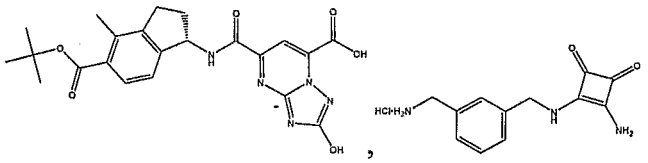
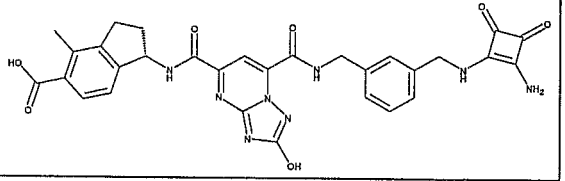
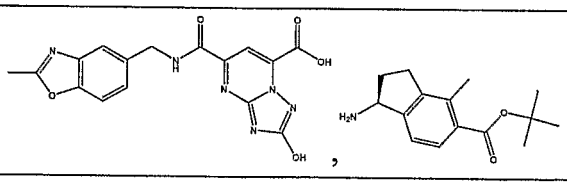
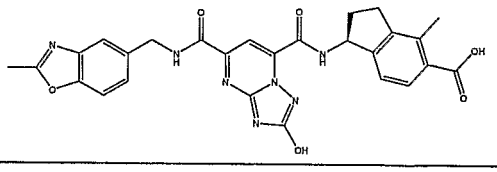
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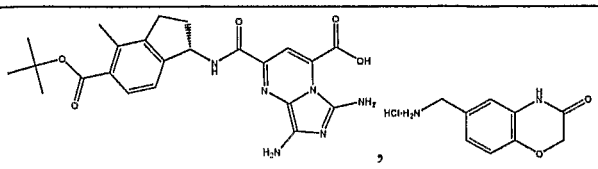
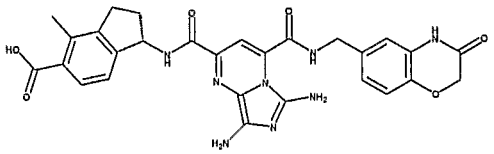
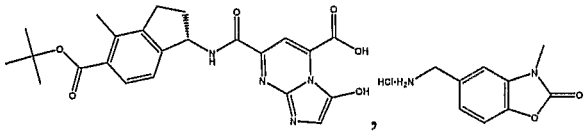
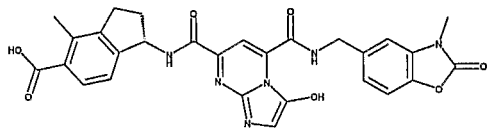
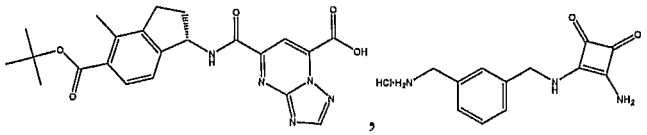
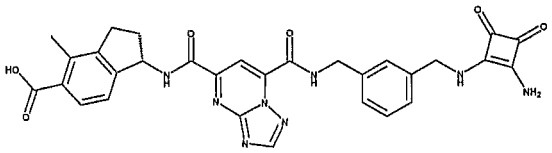
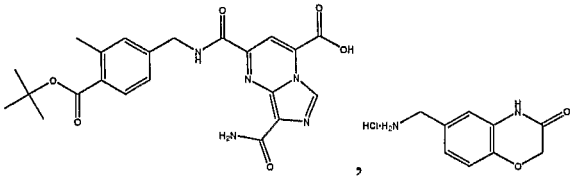
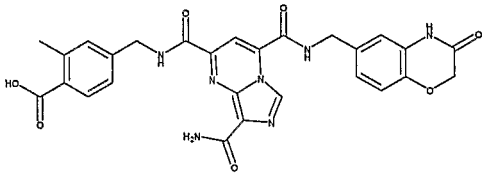
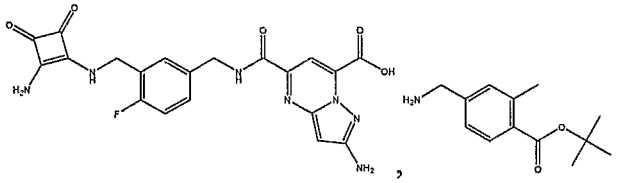
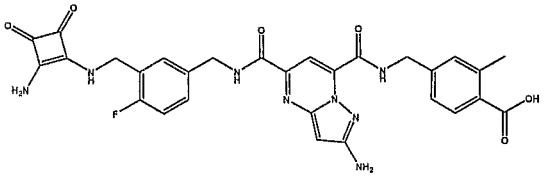
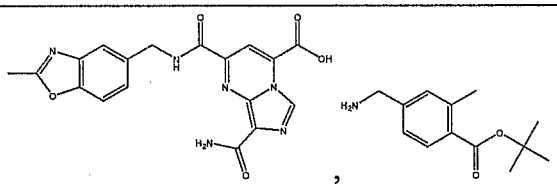
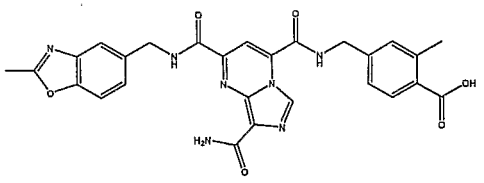
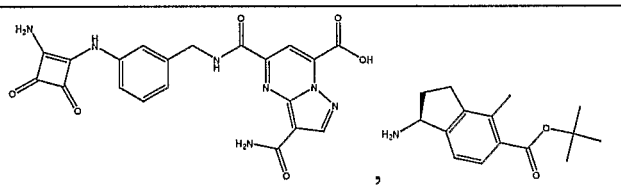
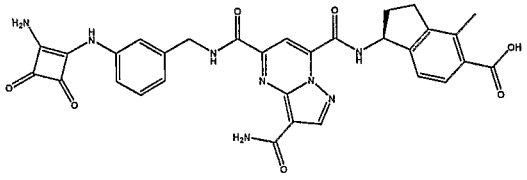
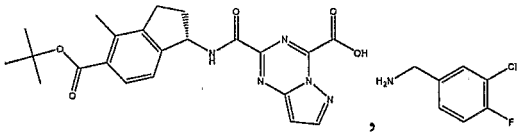
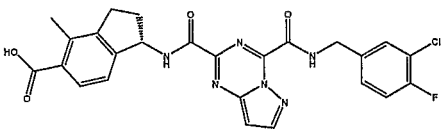
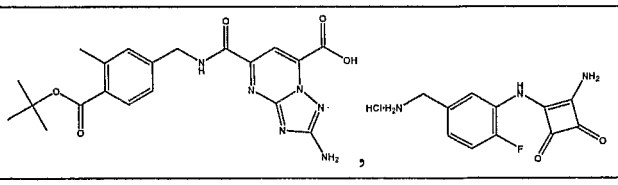
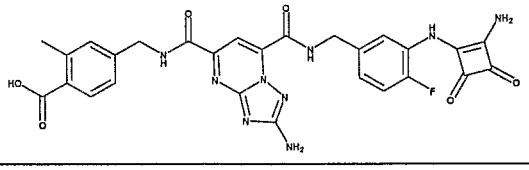
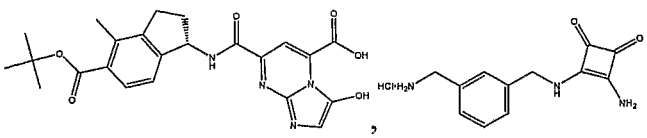
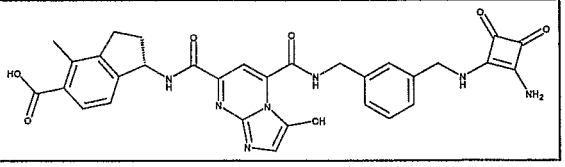
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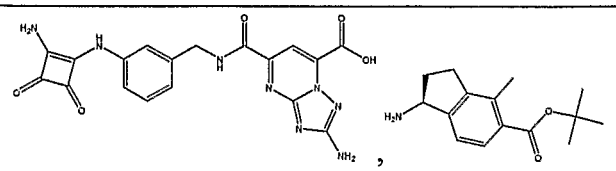
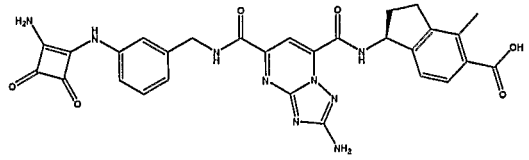
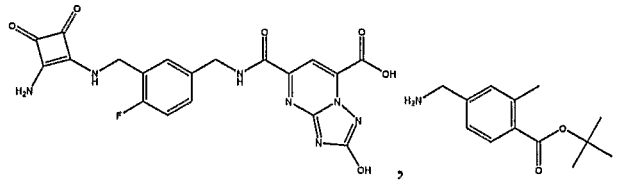
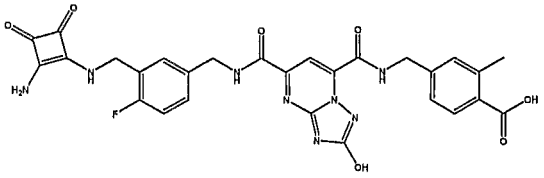
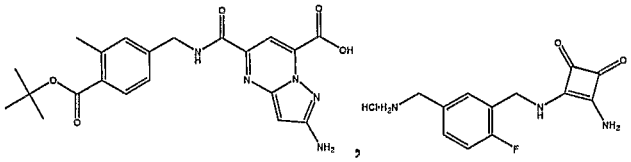
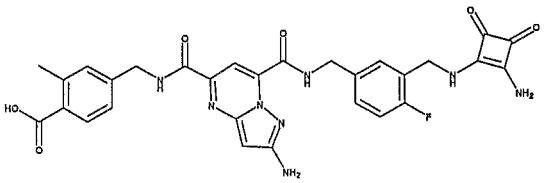
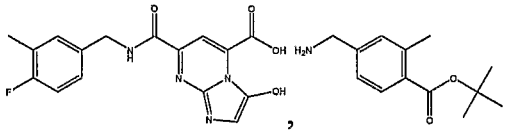
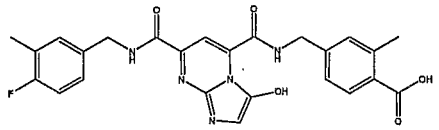
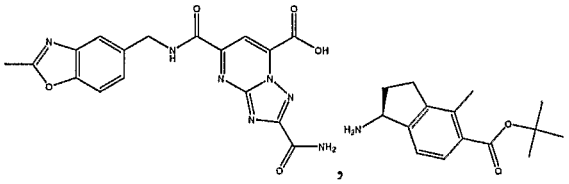
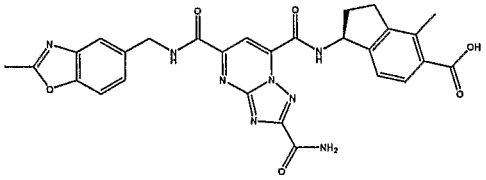
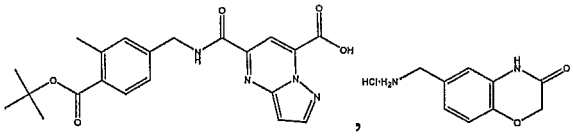
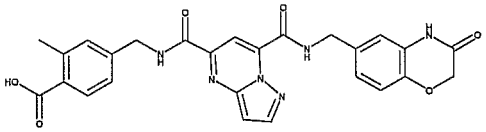
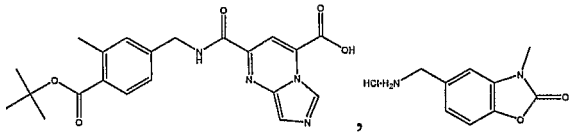
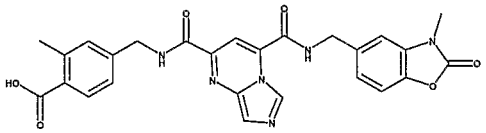
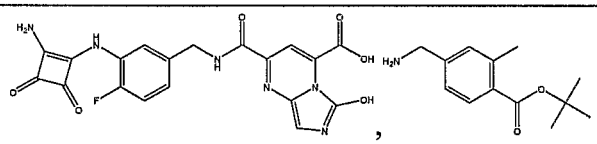
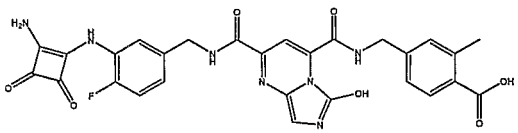
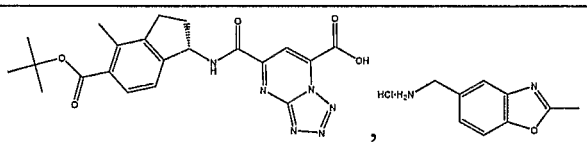
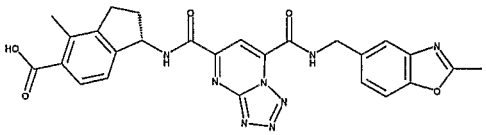
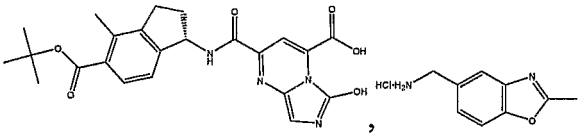
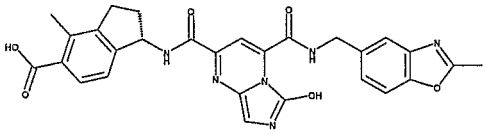
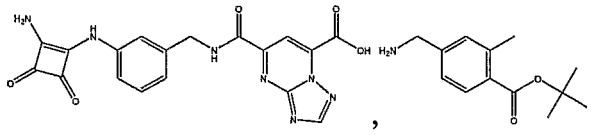
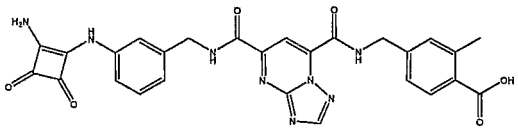
Examples 970-1149

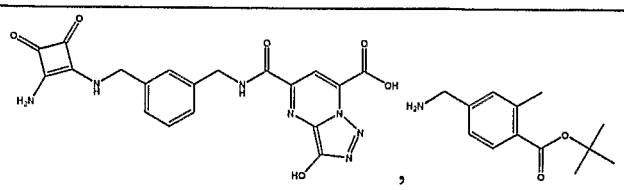
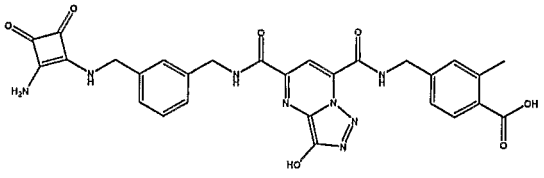
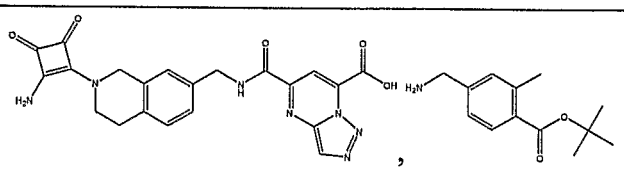
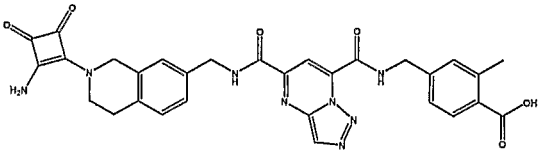
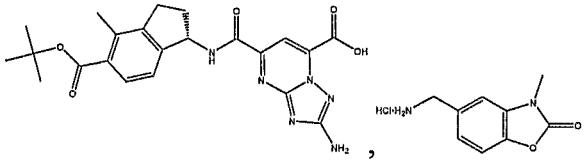
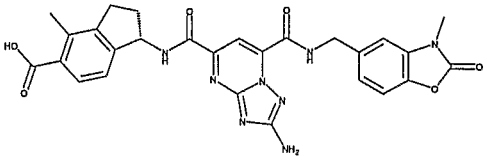
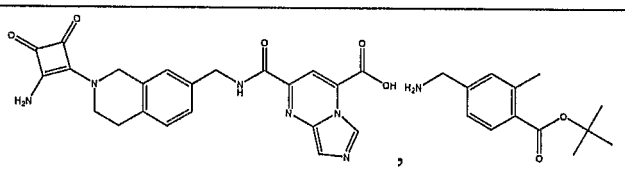
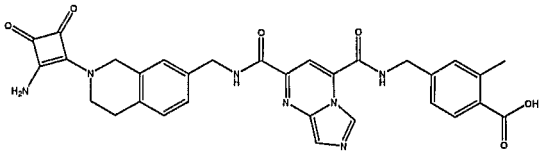
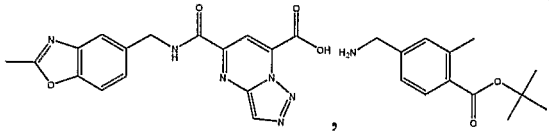
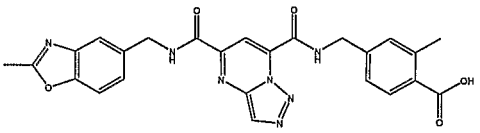
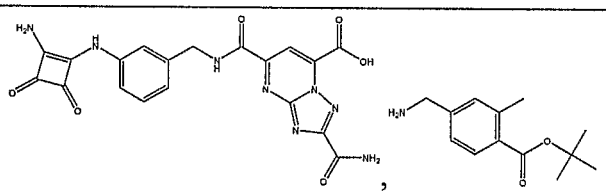
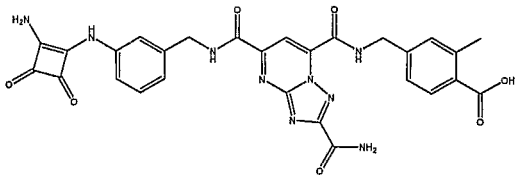
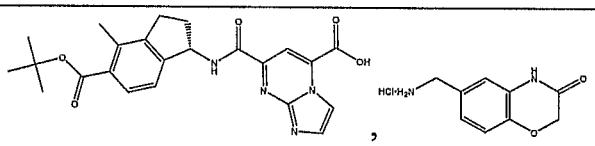
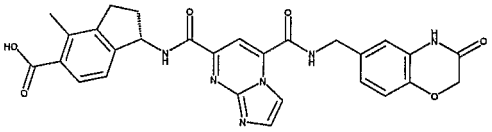
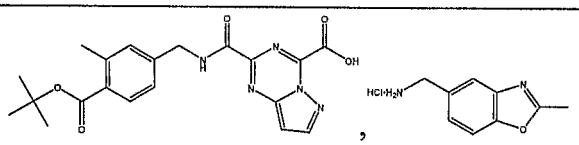
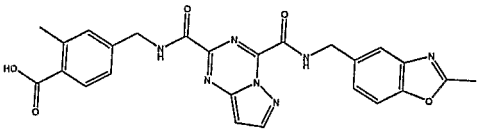
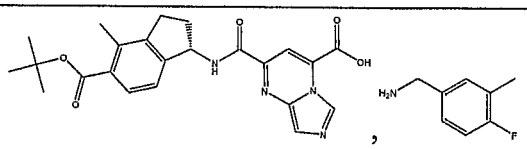
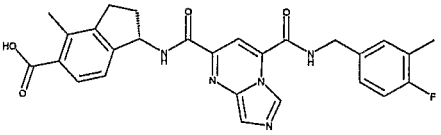
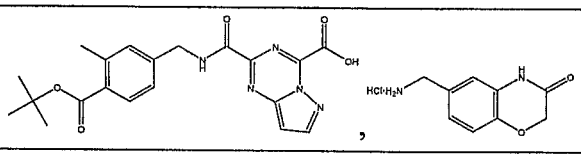
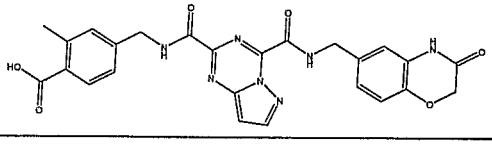
[0594] If one were to follow similar procedures as described in the Examples 1, 2, 3, 4, 5, 6 or 7, except using the acids and amines indicated in Table II-15 below, and if one were to treat the obtained esters similarly as described in the Example 436, the following compounds would be obtained.

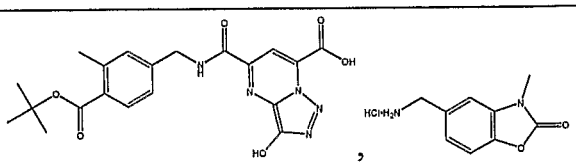
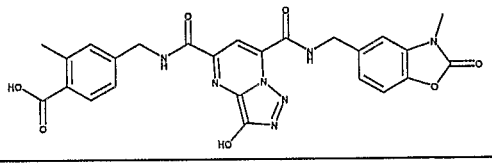
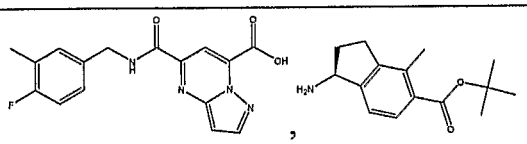
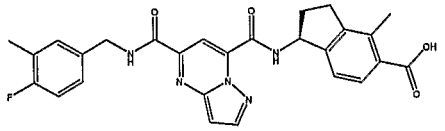
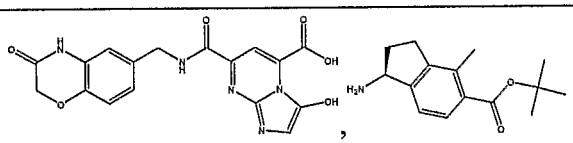
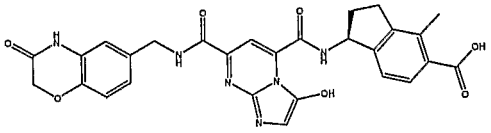
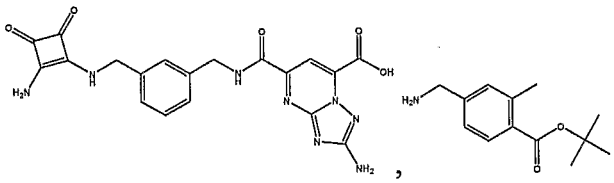
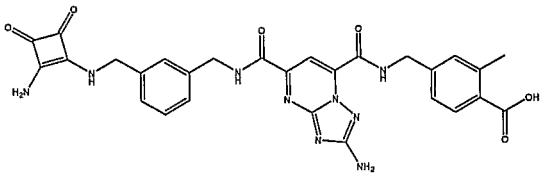
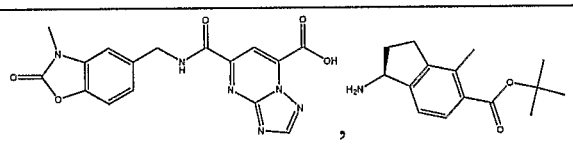
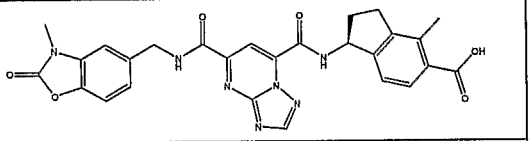
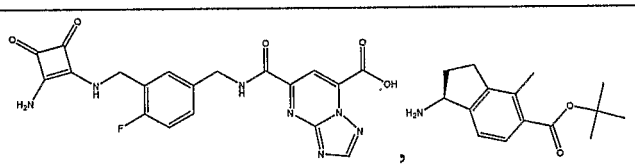
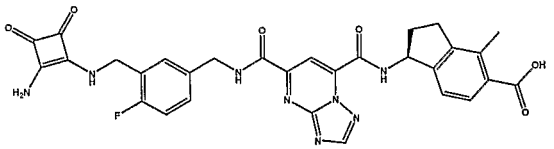
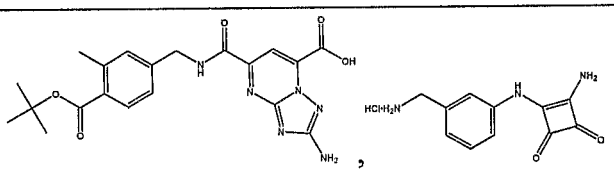
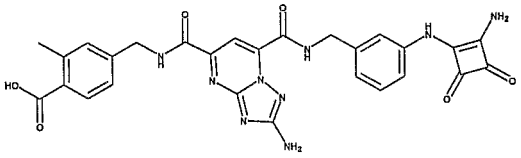
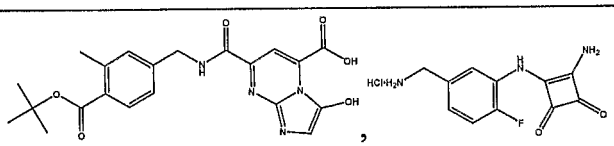
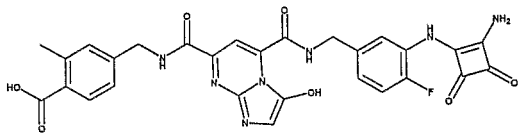
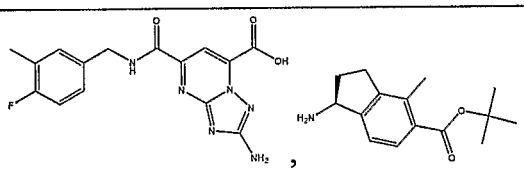
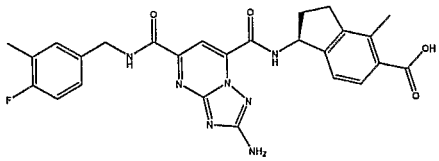
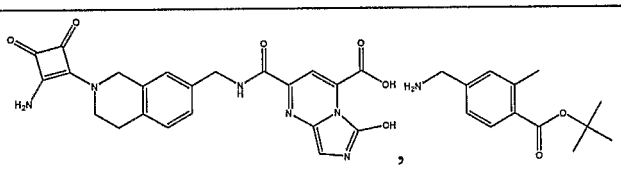
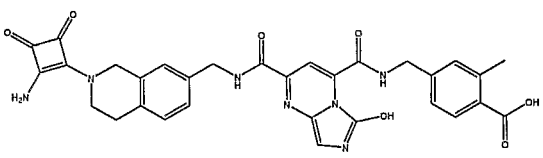
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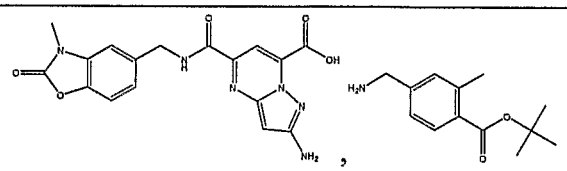
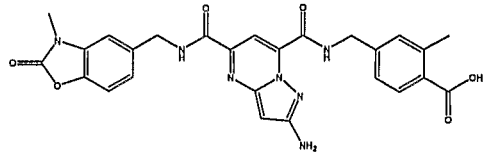
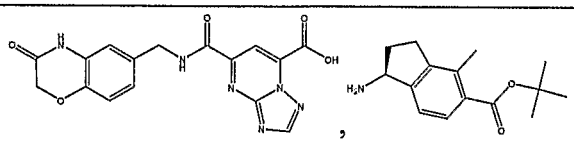
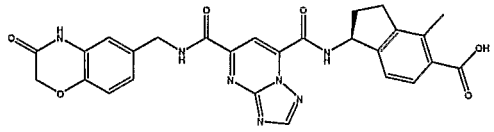
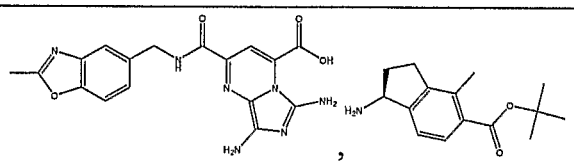
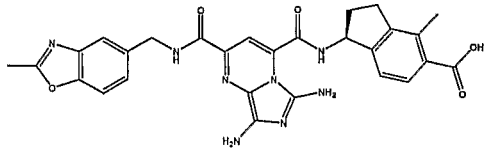
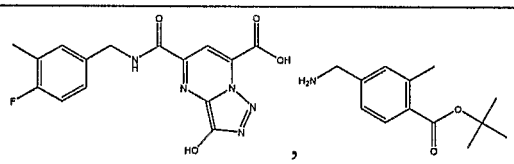
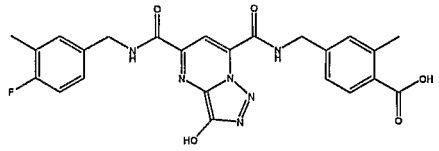
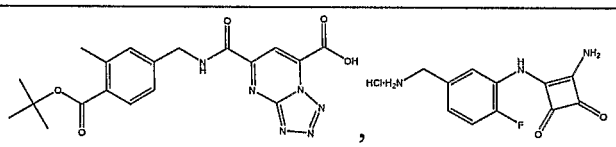
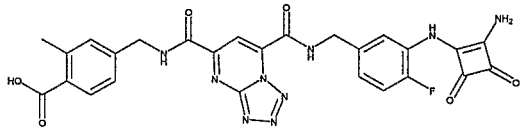
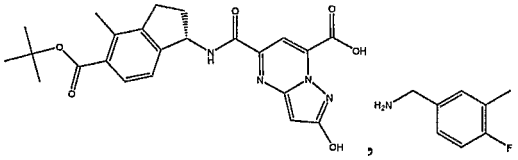
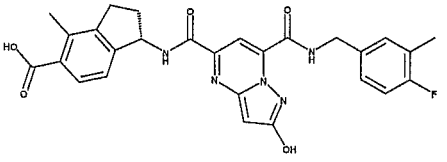
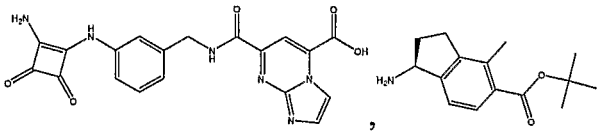
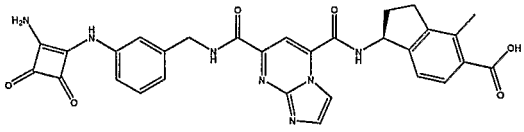
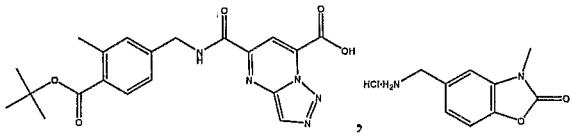
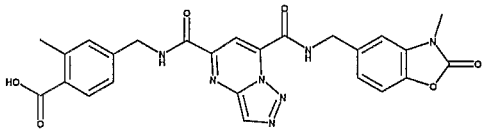
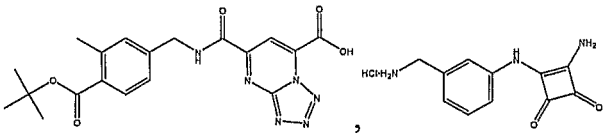
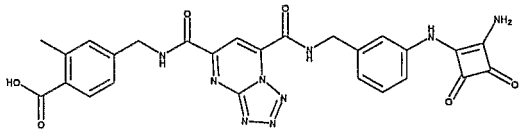
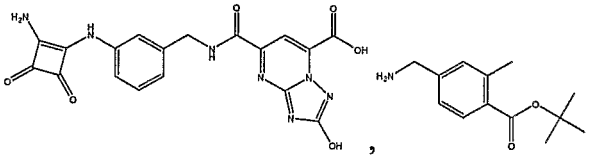
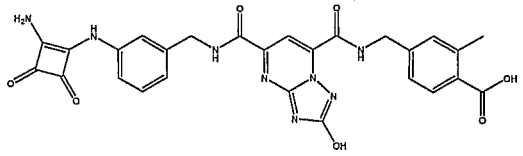
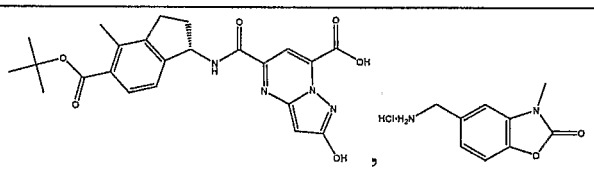
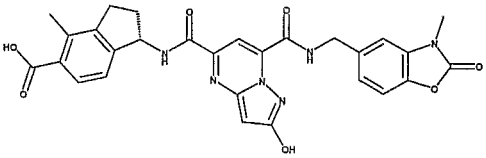
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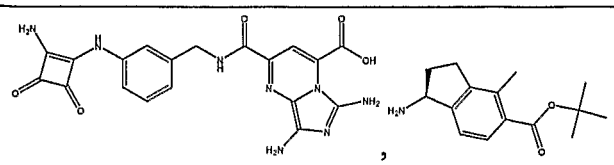
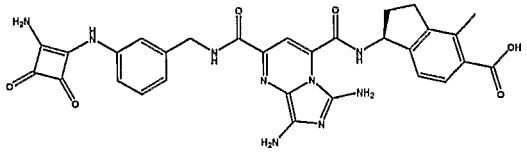
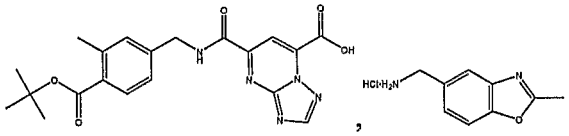
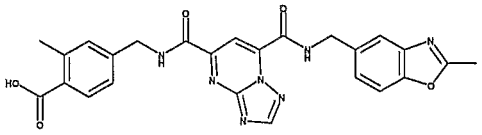
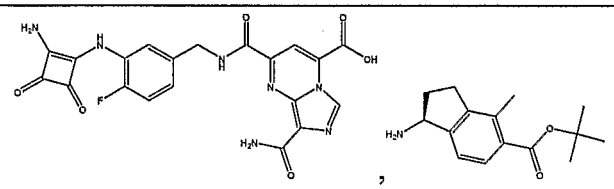
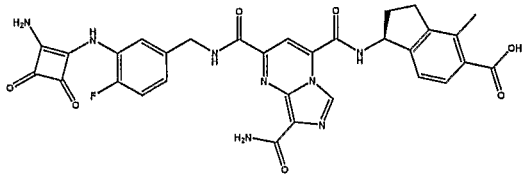
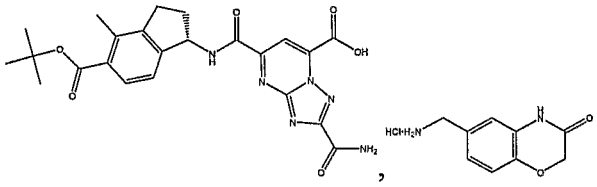
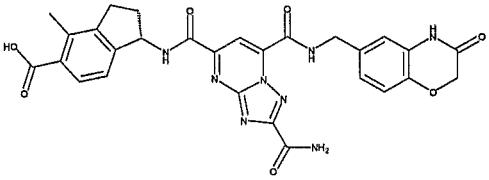
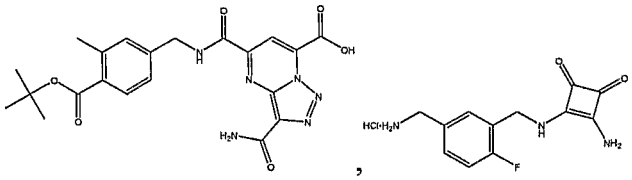
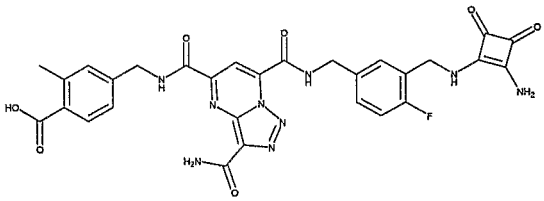
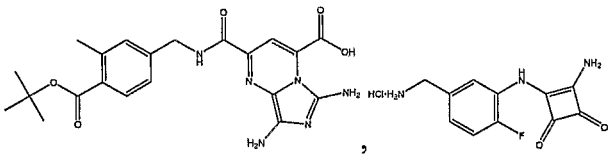
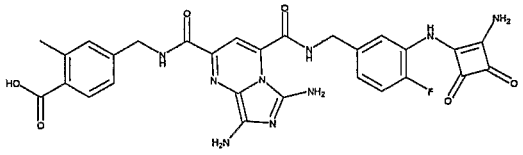
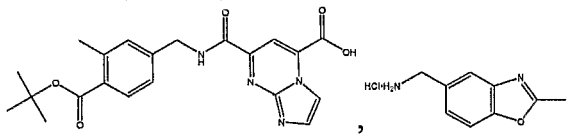
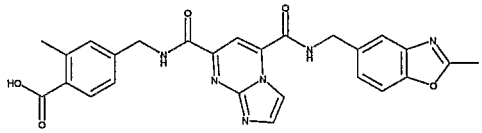
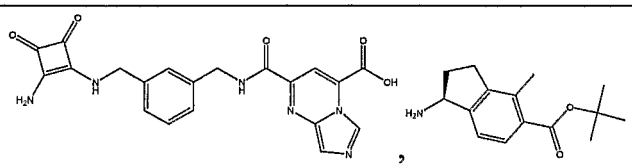
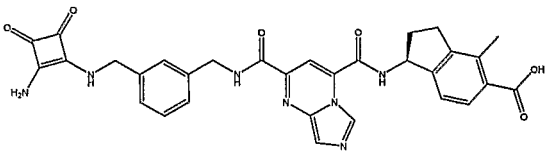
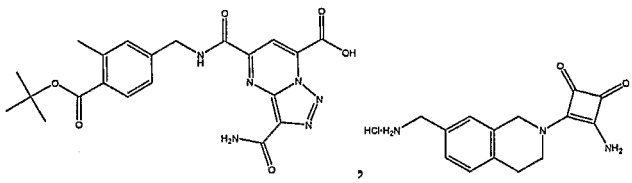
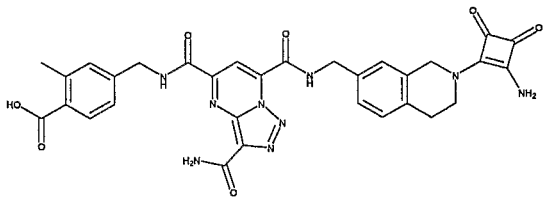
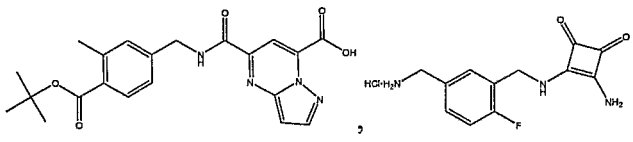
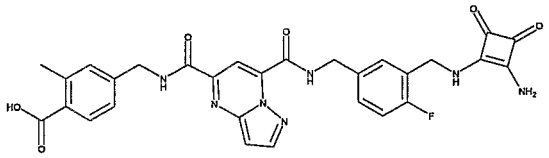
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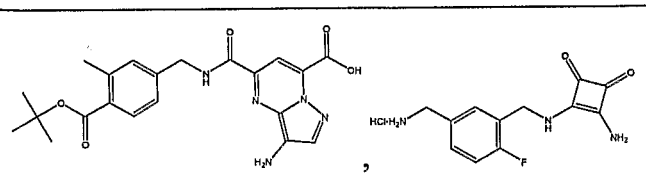
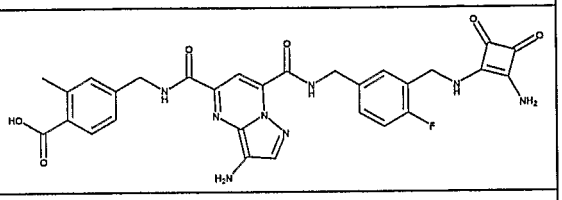
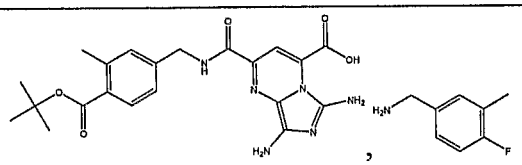
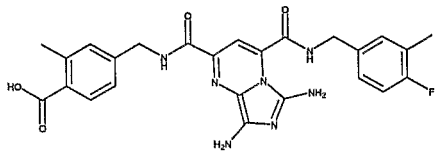
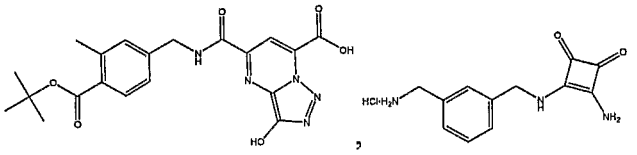
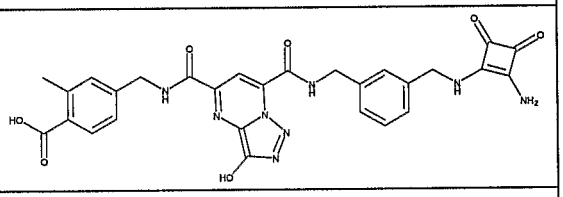
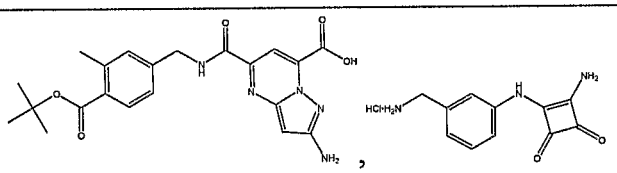
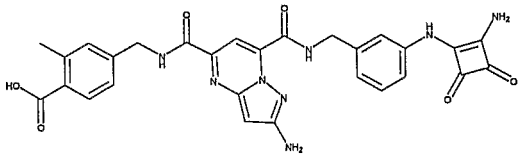
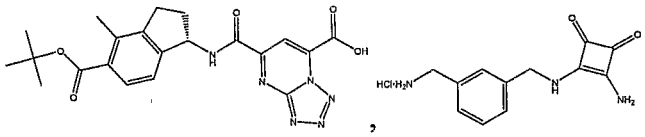
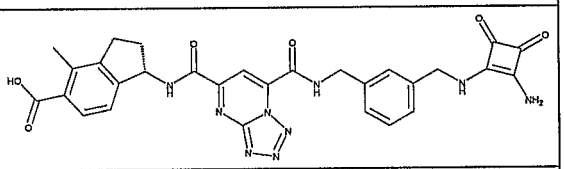
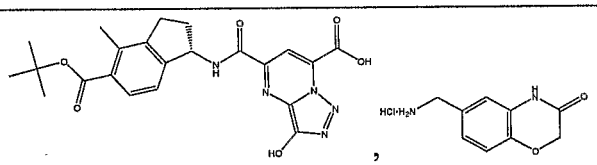
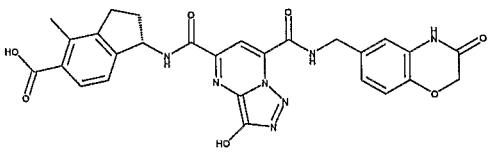
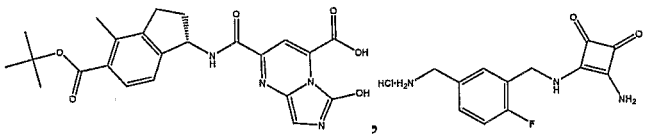
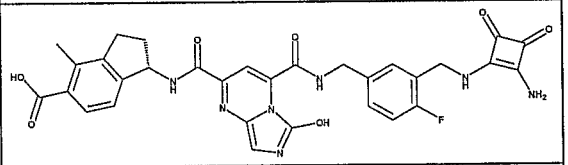
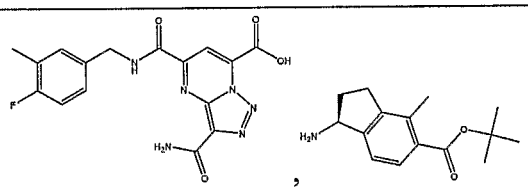
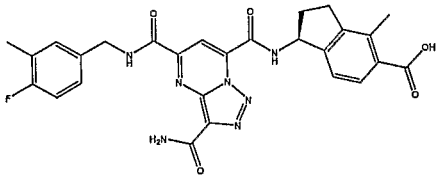
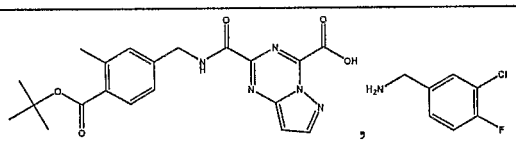
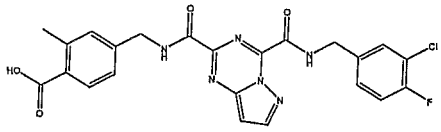
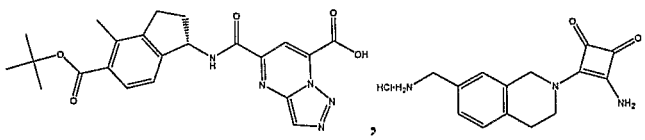
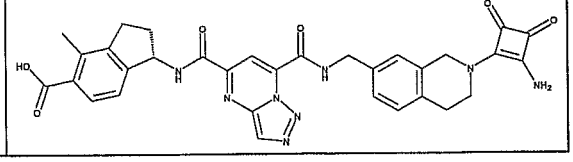
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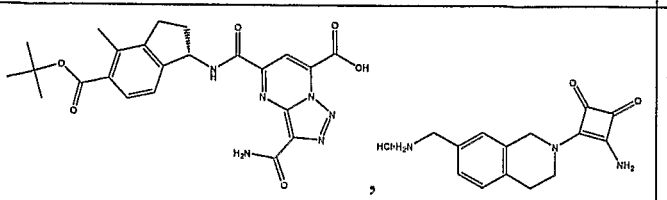
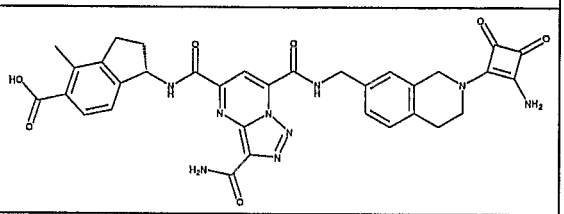
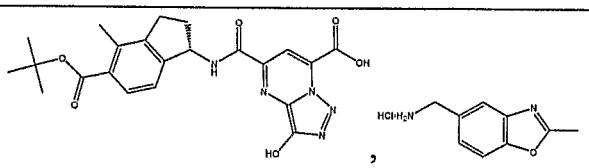
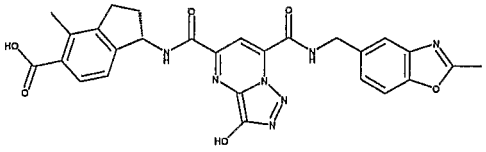
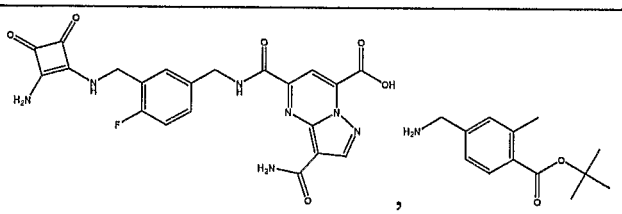
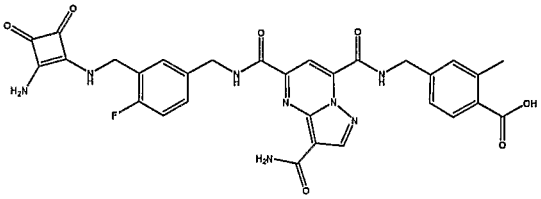
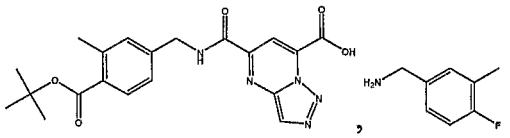
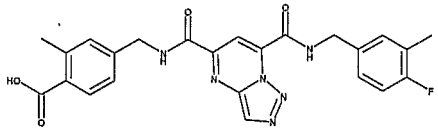
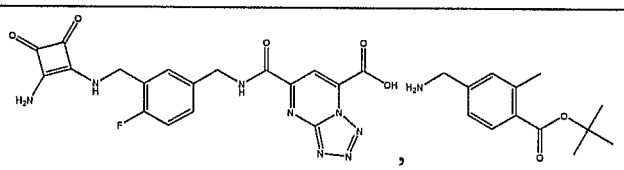
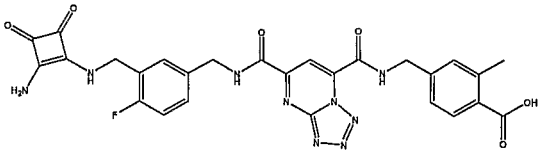
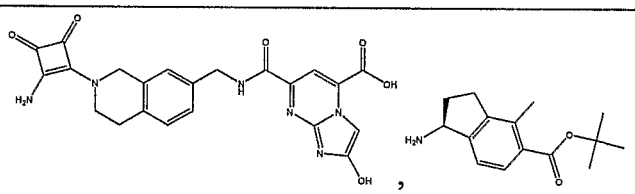
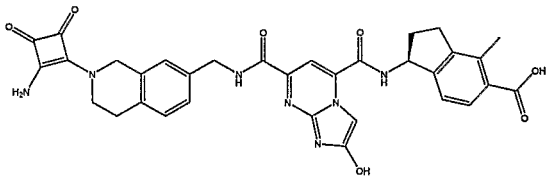
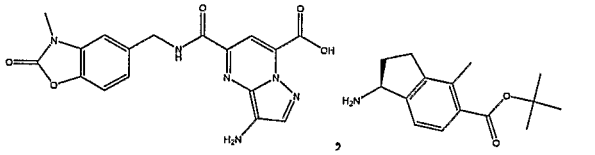
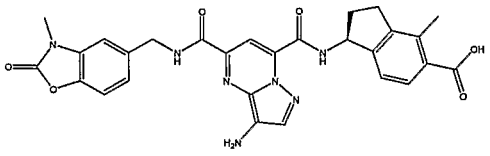
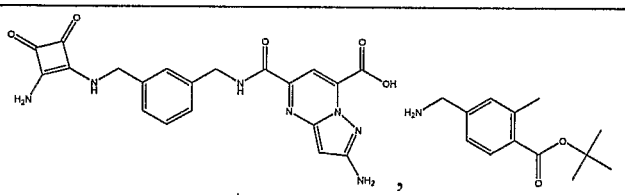
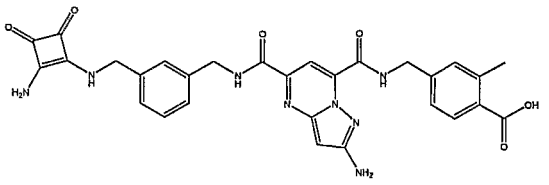
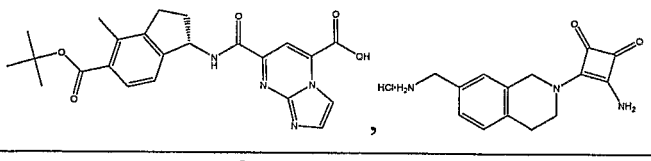
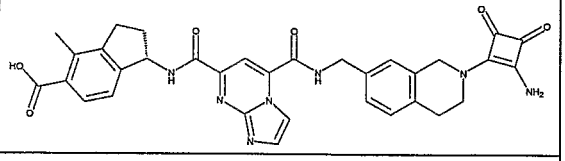
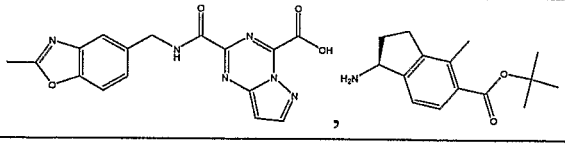
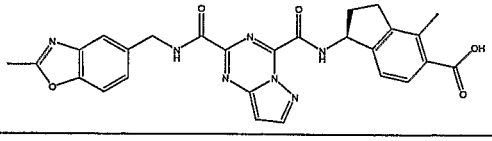
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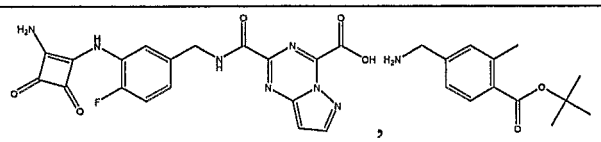
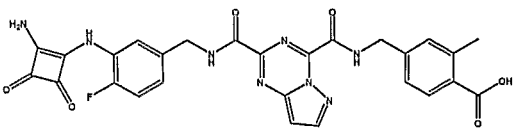
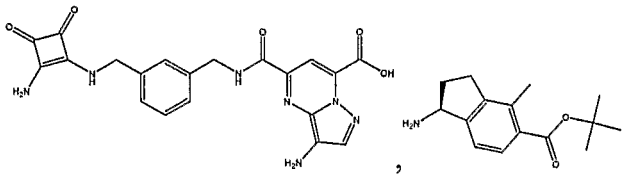
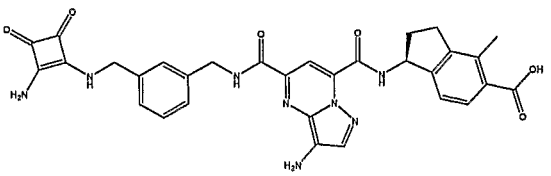
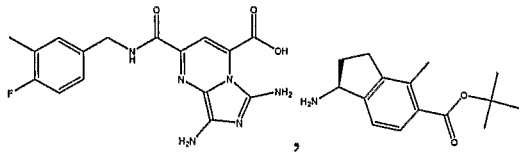
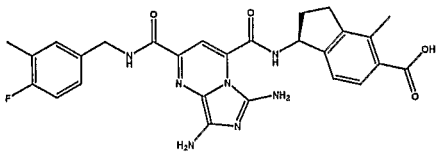
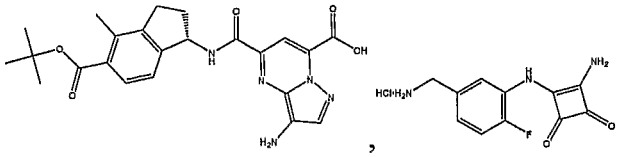
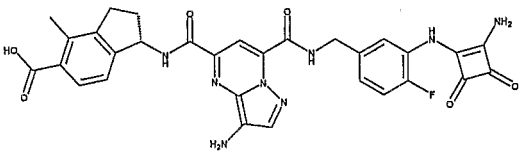
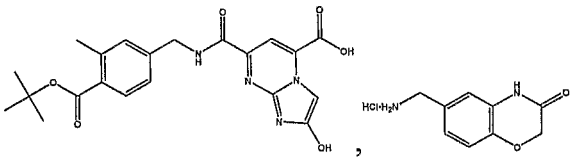
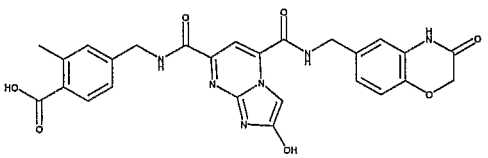
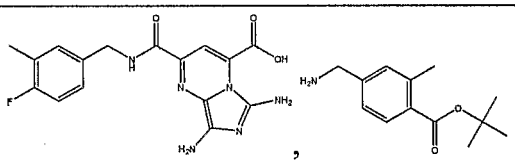
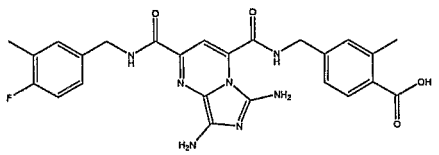
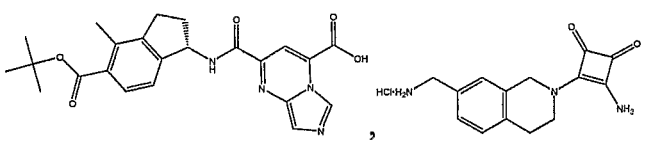
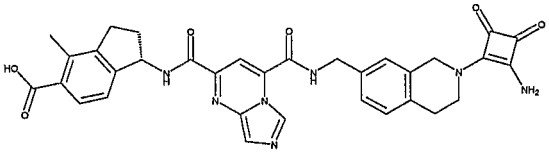
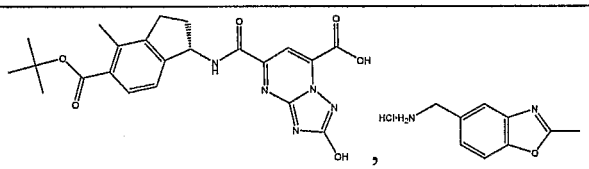
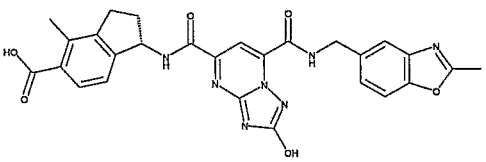
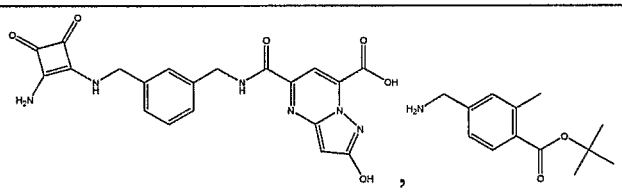
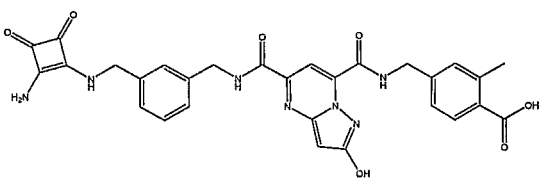
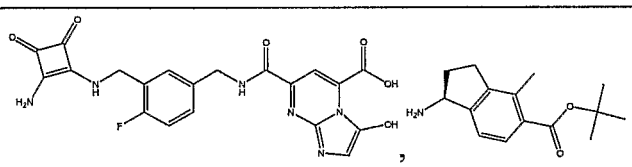
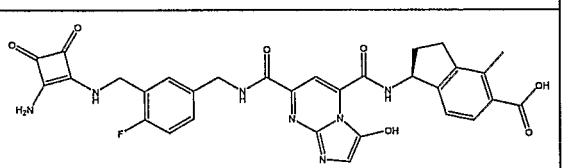
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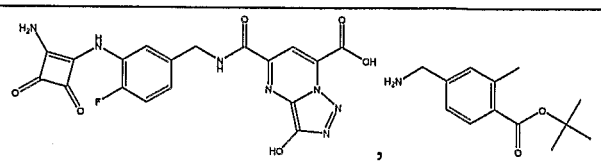
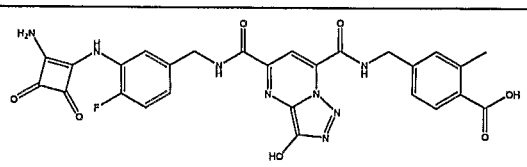
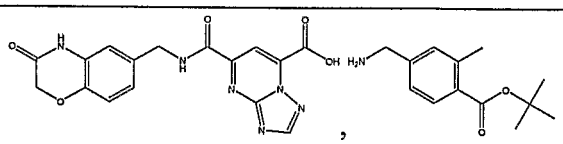
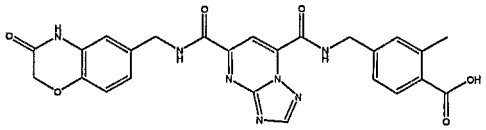
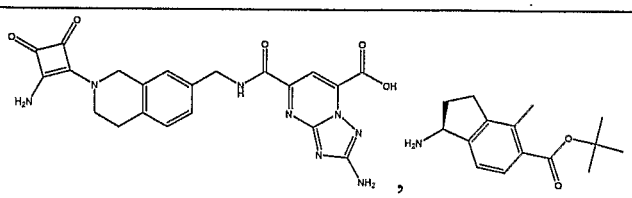
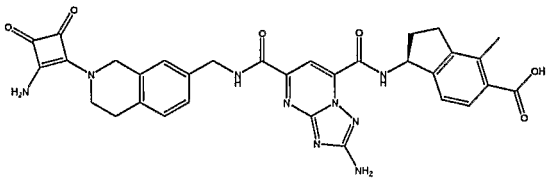
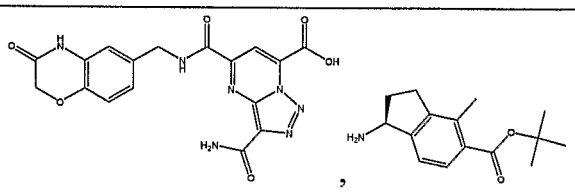
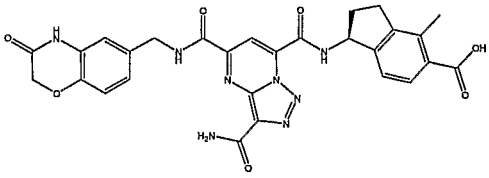
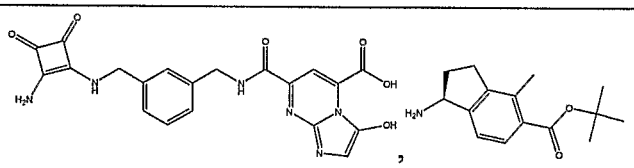
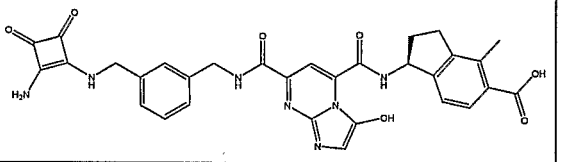
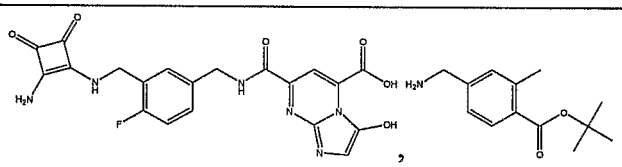
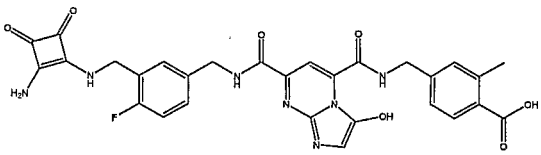
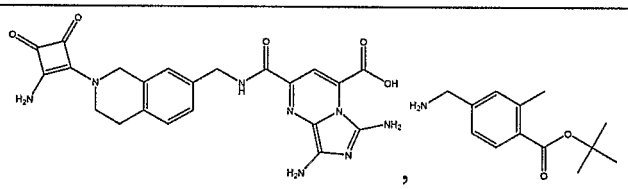
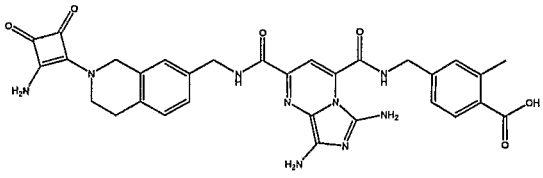
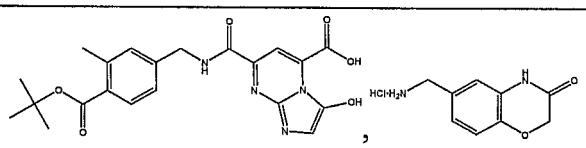
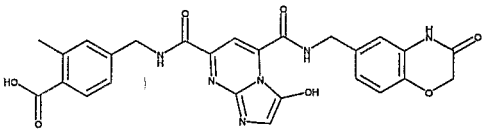
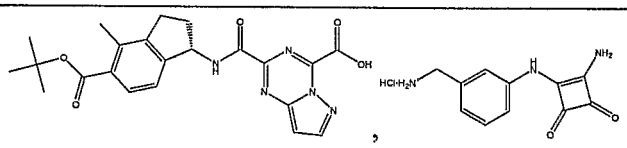
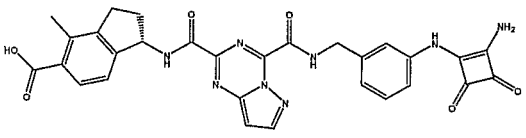
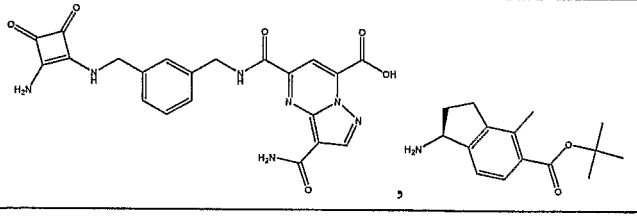
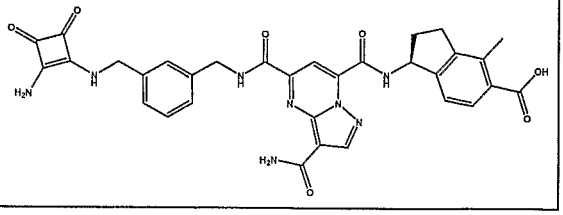
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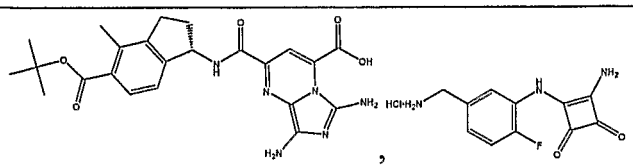
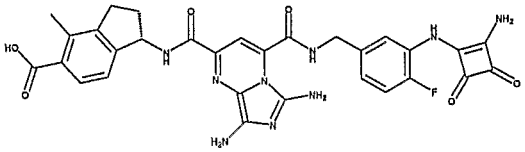
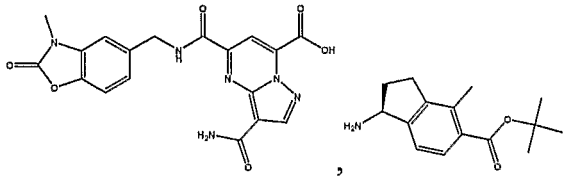
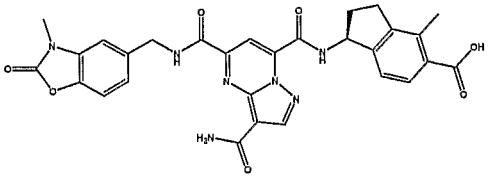
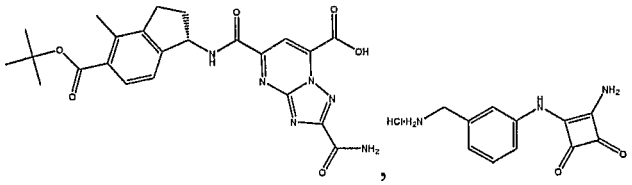
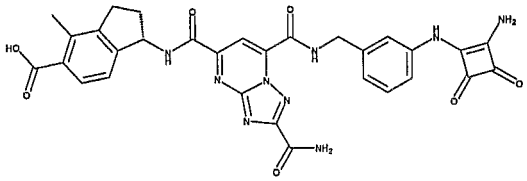
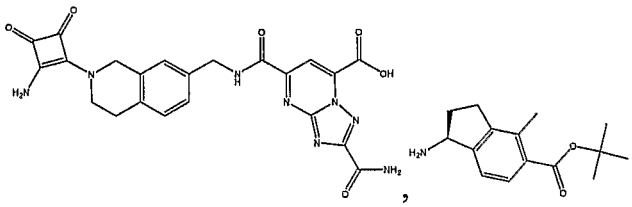
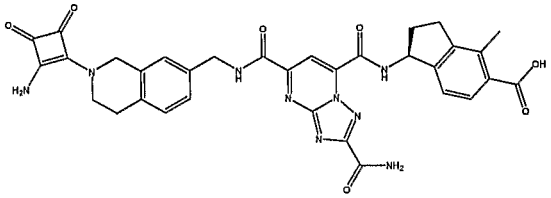
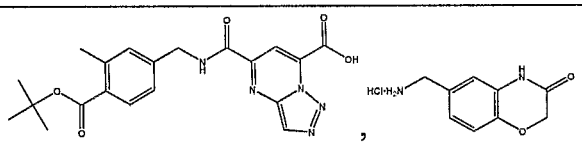
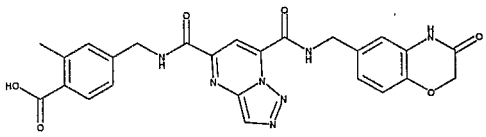
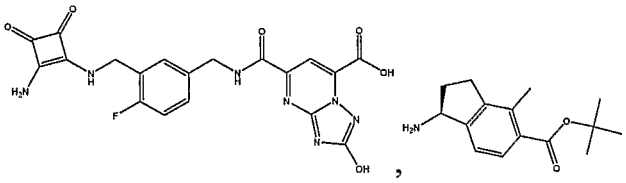
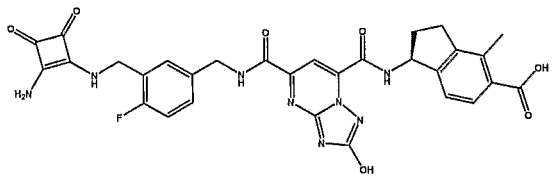
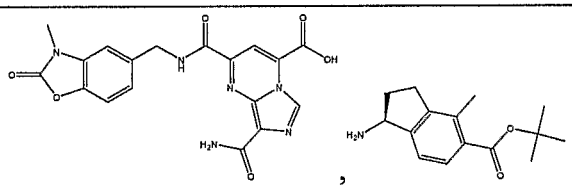
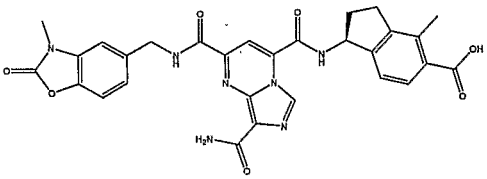
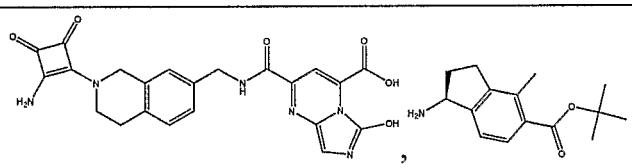
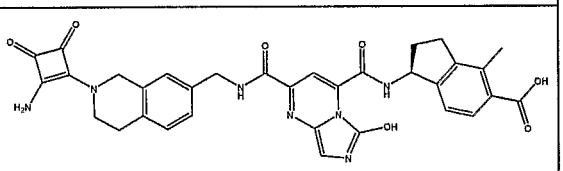
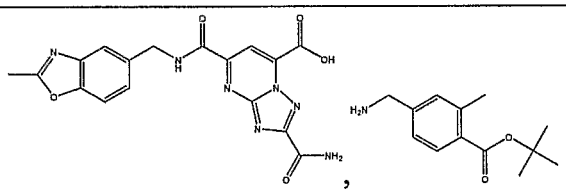
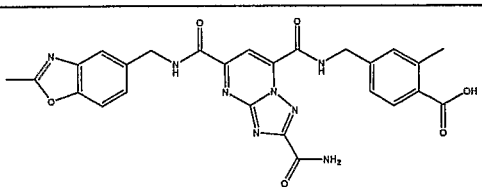
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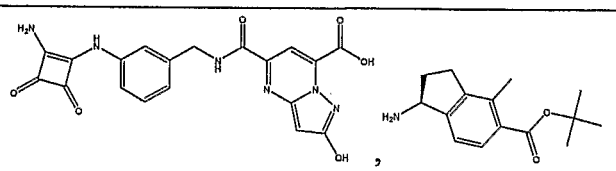
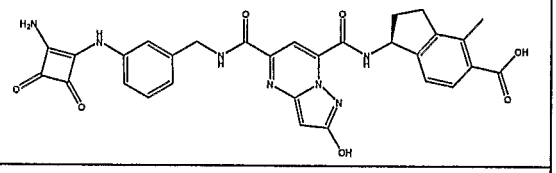
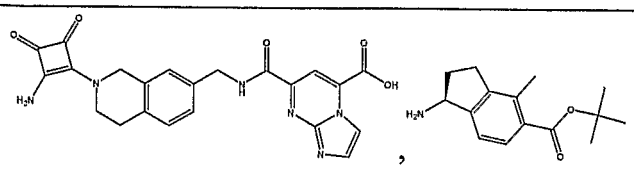
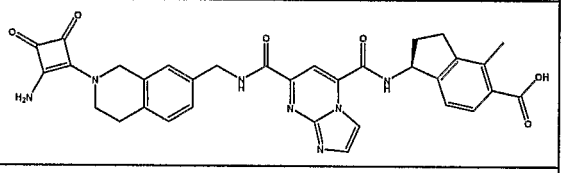
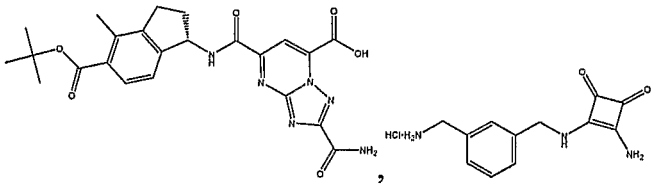
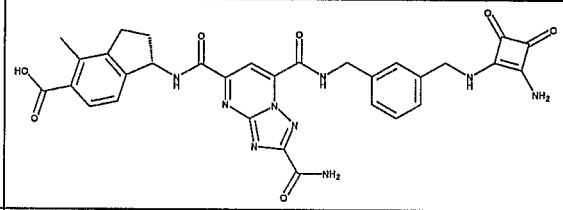
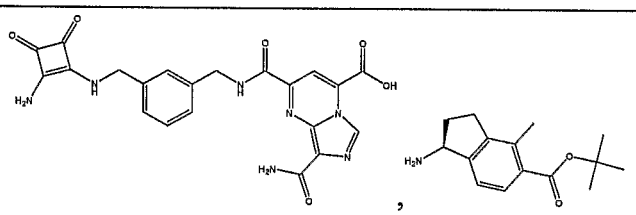
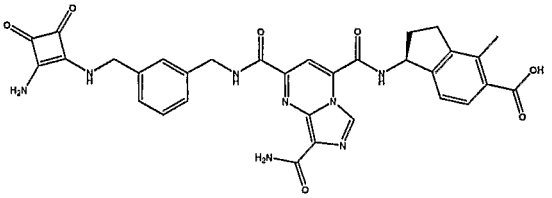
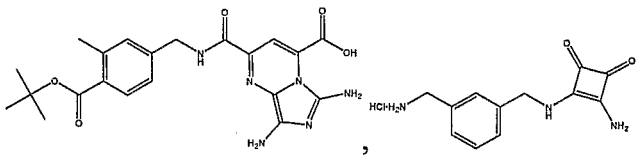
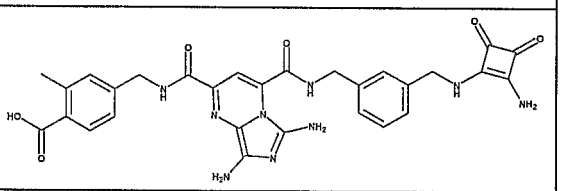
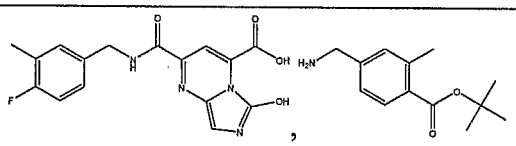
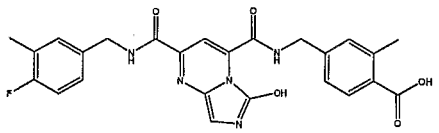
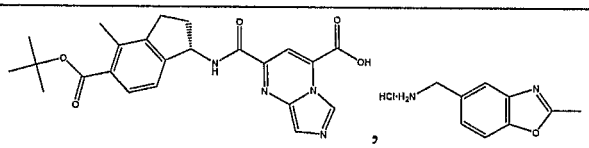
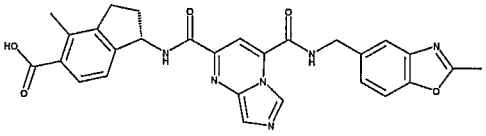
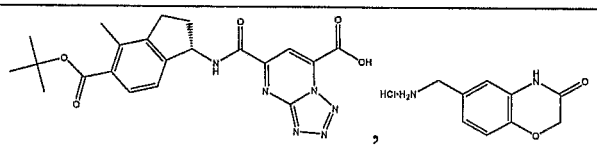
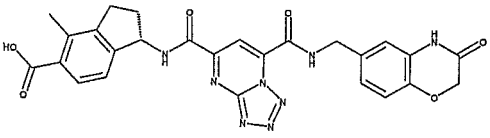
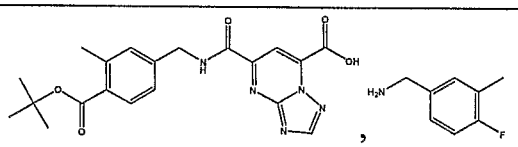
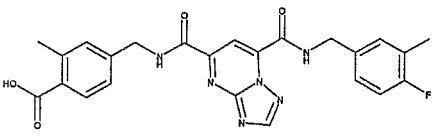
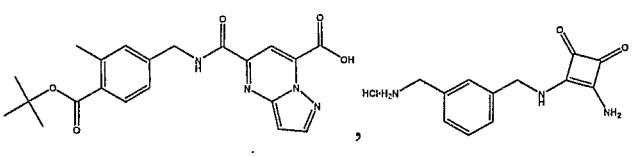
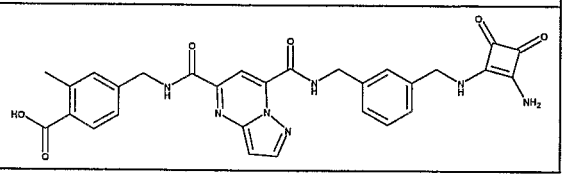
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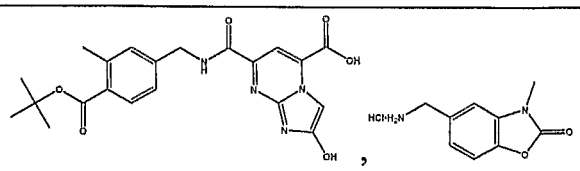
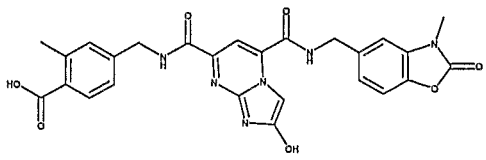
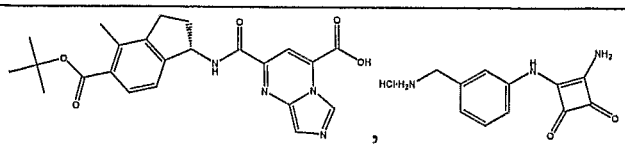
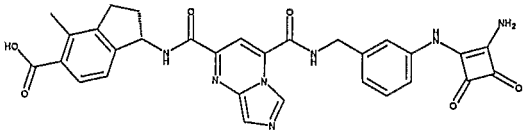
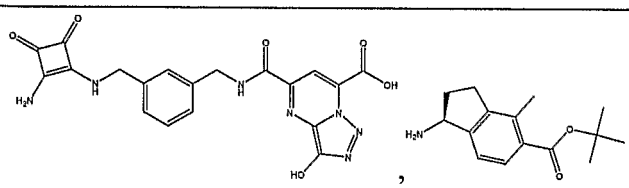
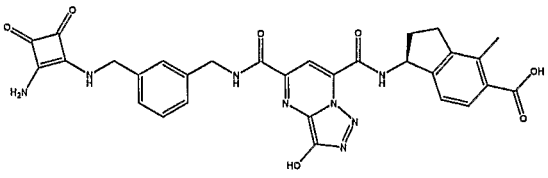
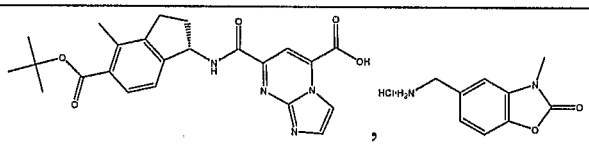
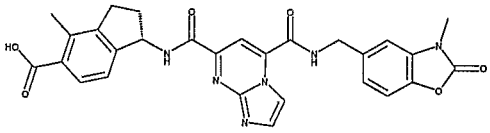
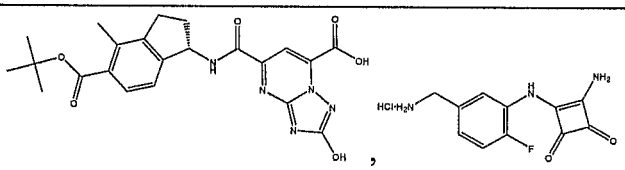
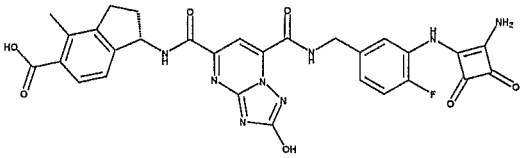
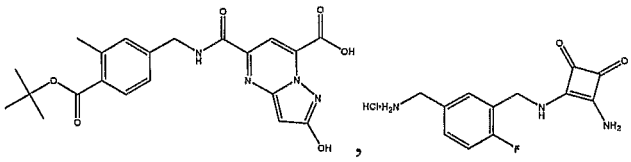
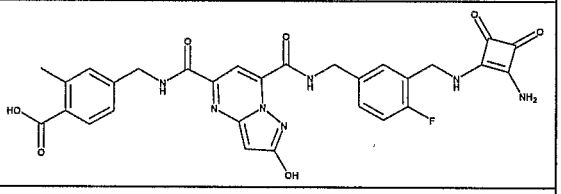
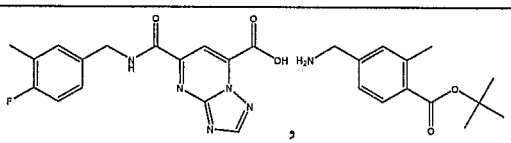
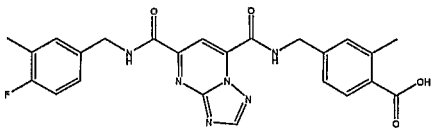
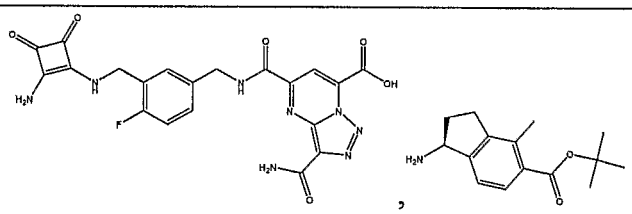
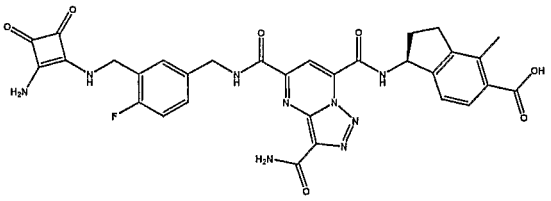
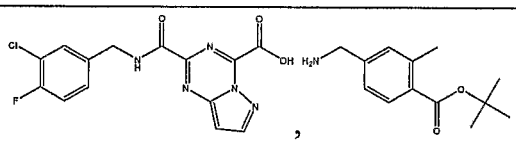
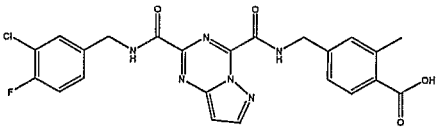
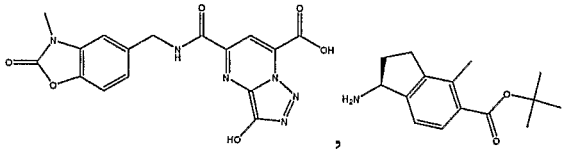
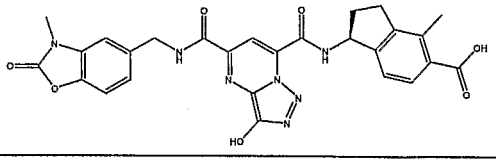
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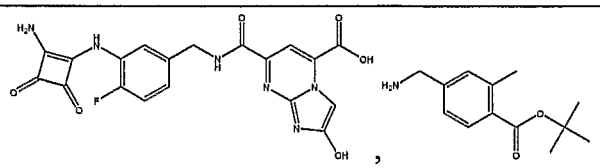
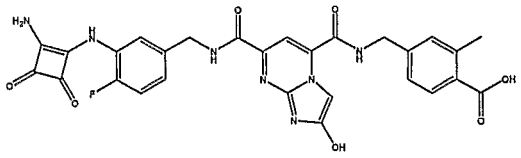
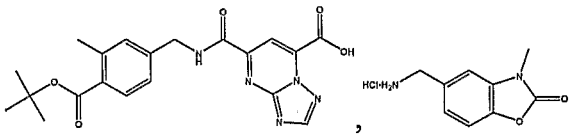
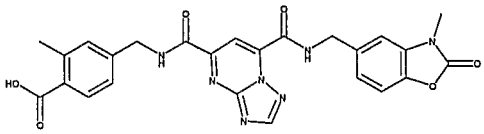
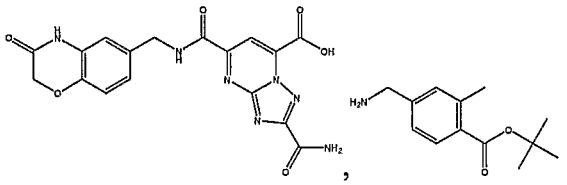
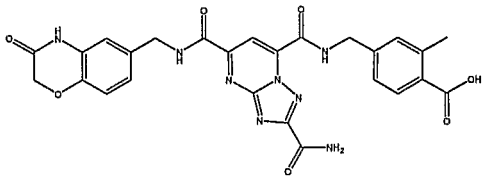
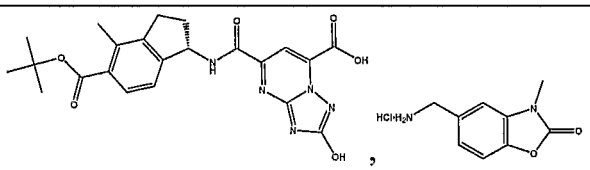
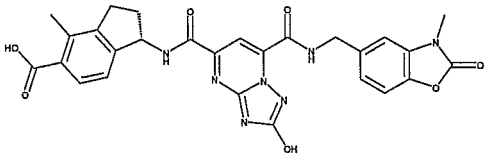
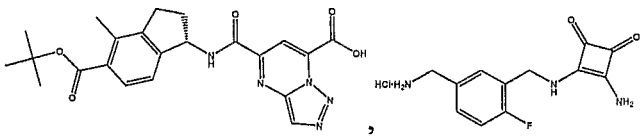
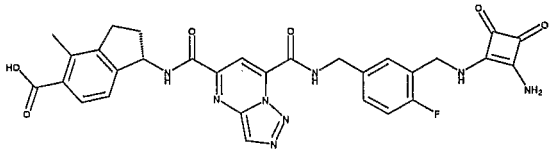
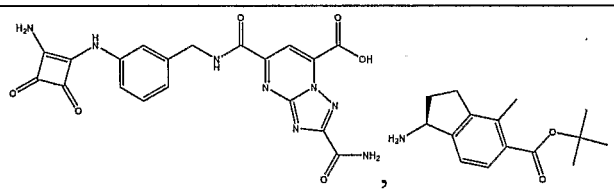
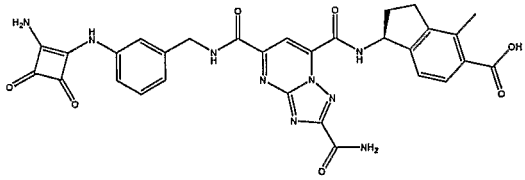
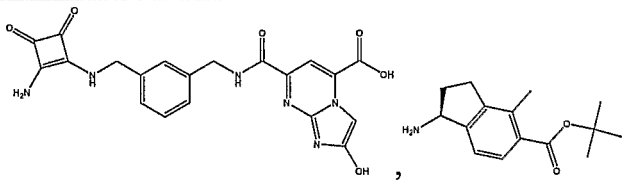
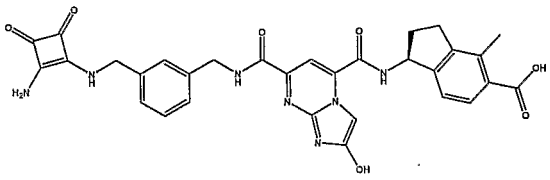
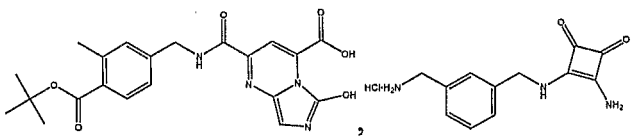
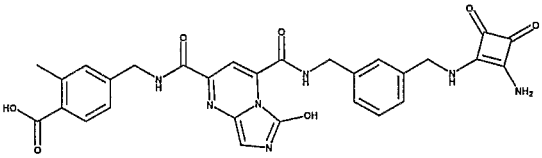
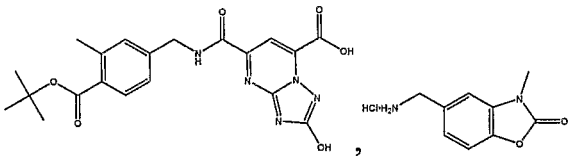
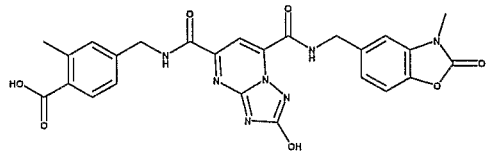
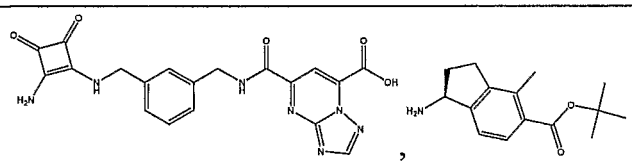
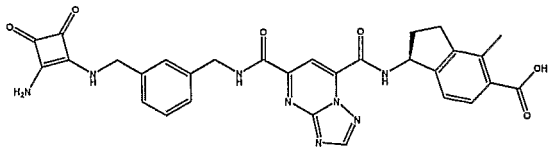
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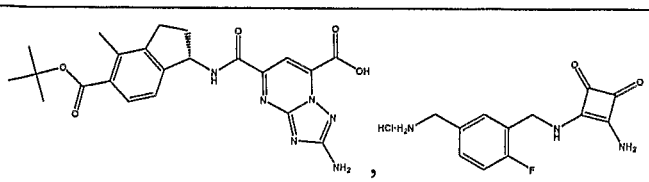
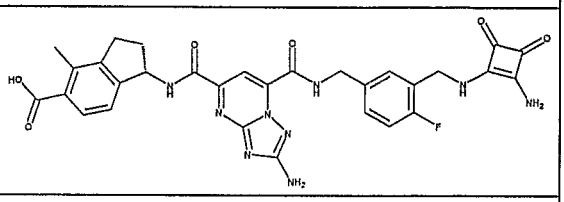
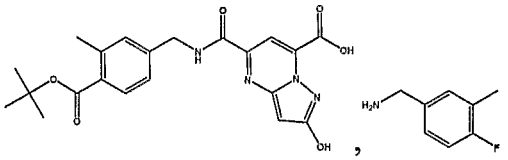
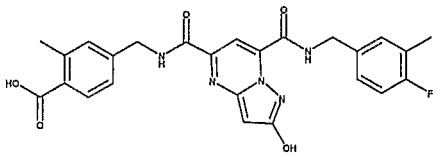
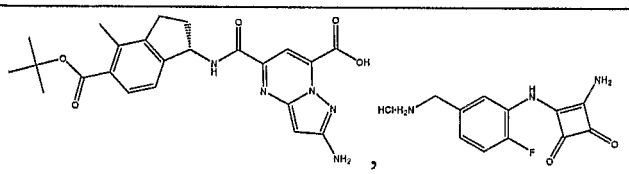
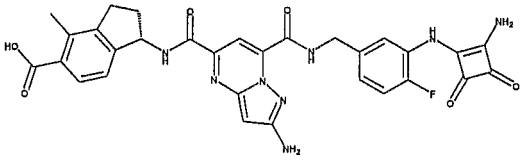
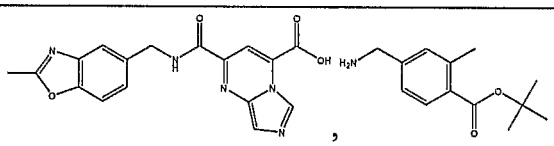
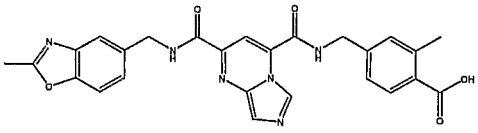
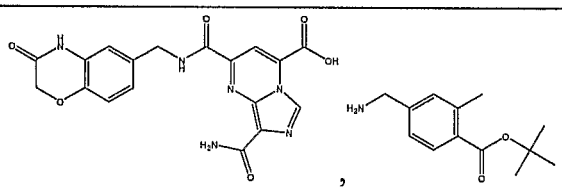
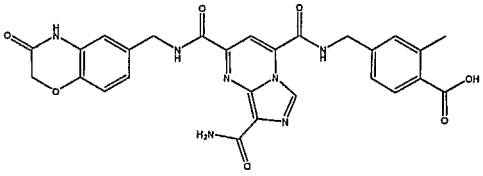
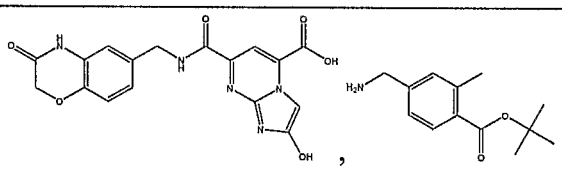
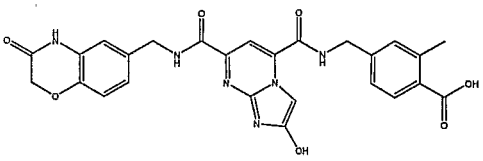
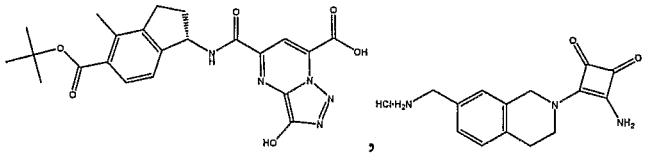
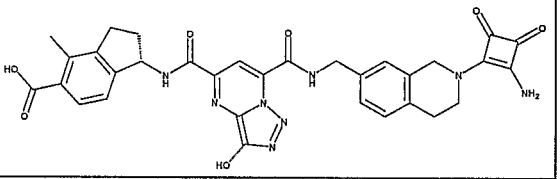
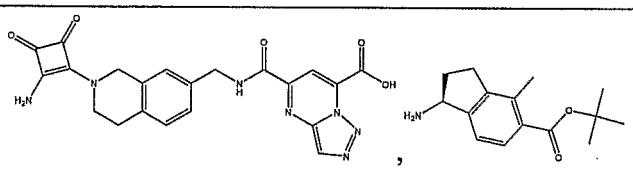
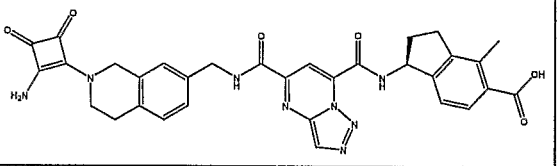
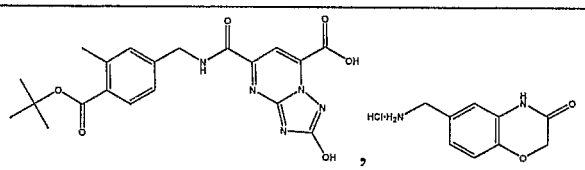
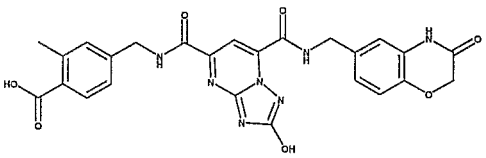
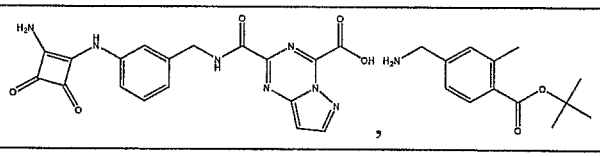
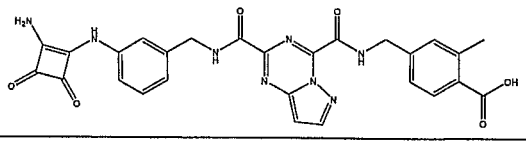
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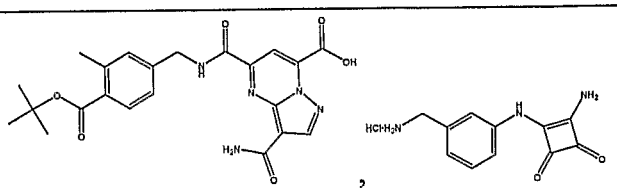
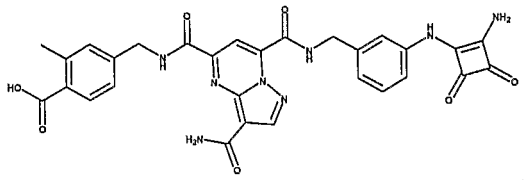
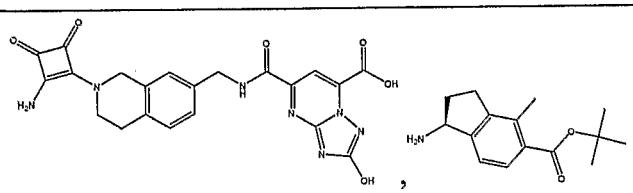
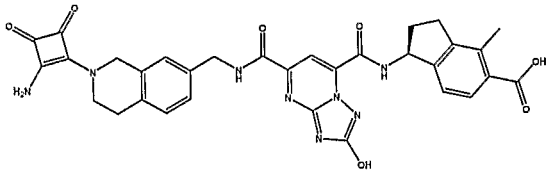
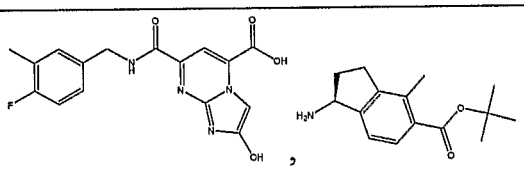
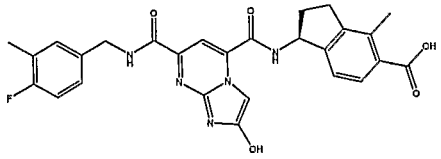
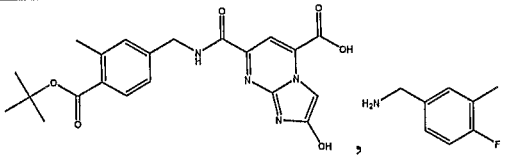
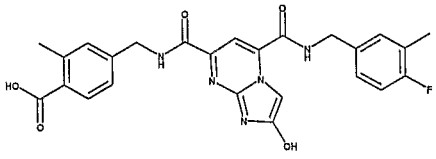
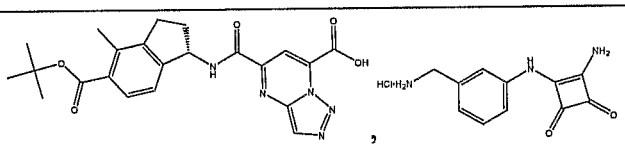
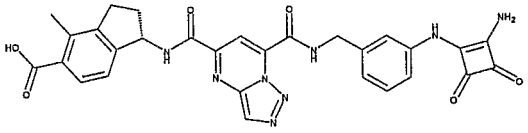
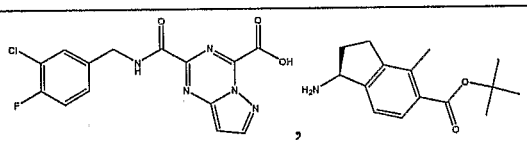
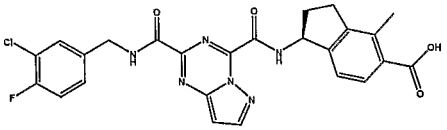
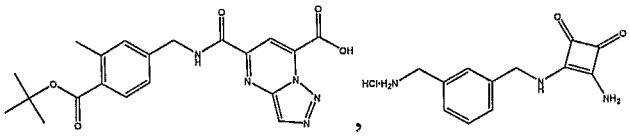
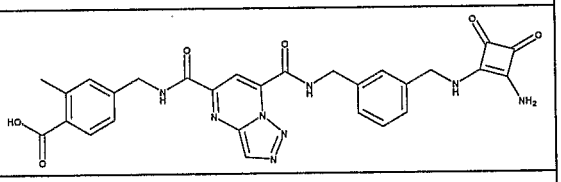
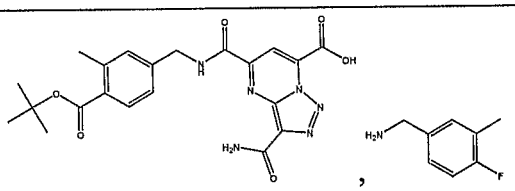
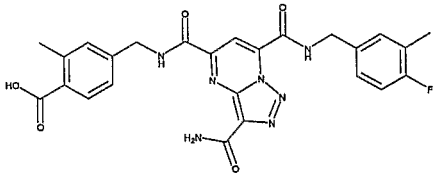
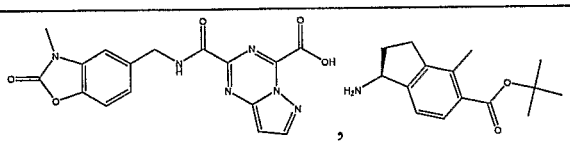
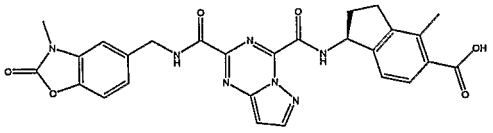
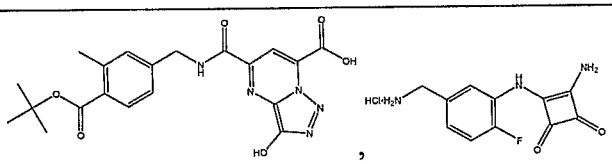
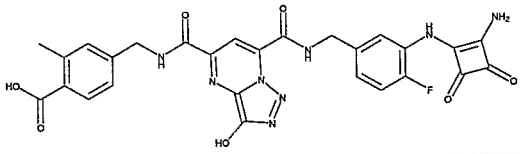
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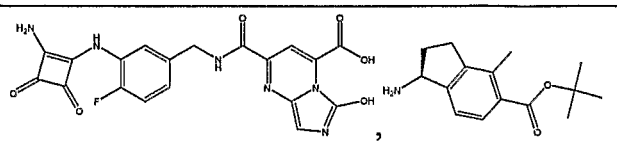
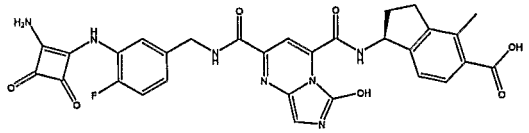
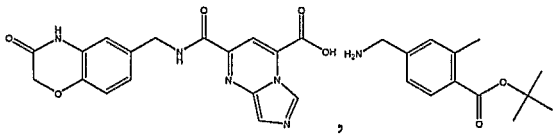
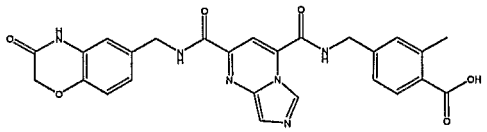
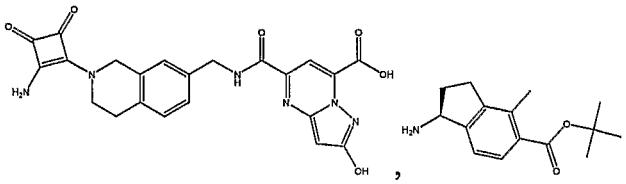
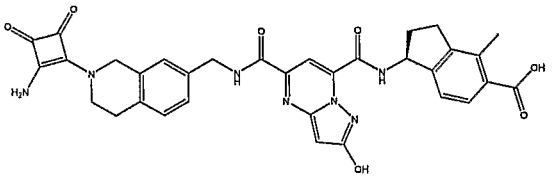
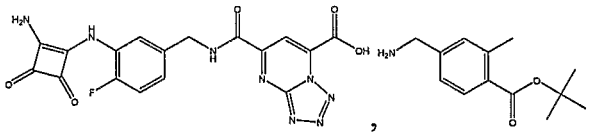
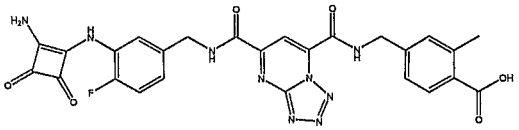
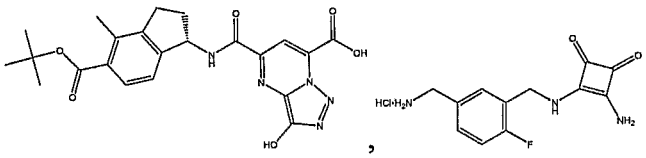
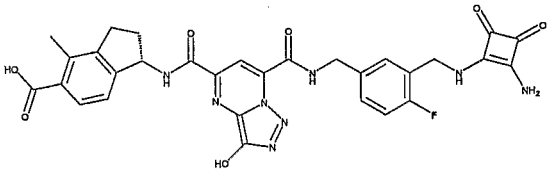
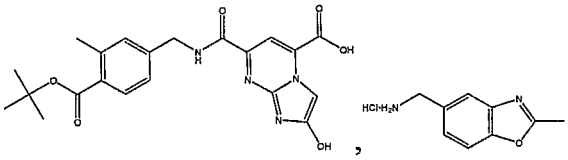
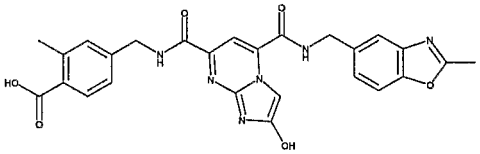
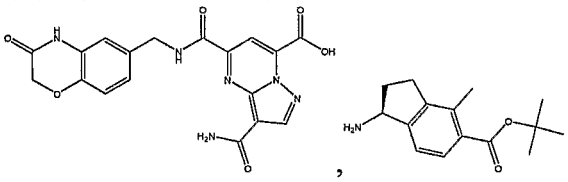
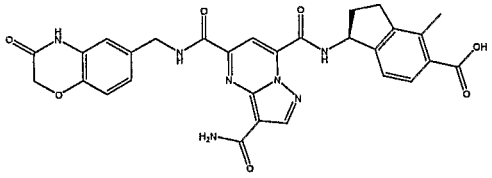
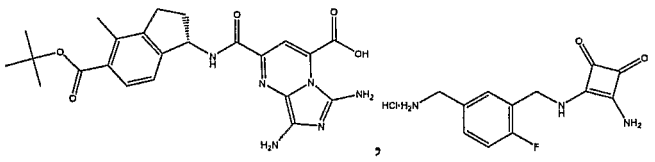
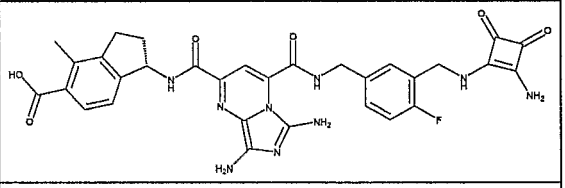
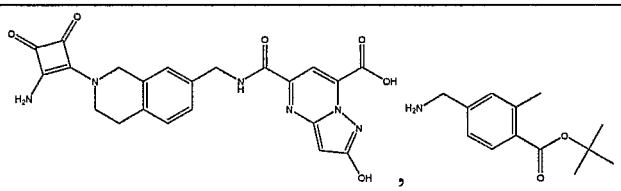
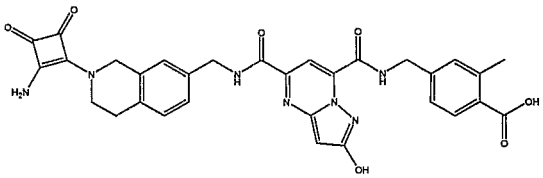
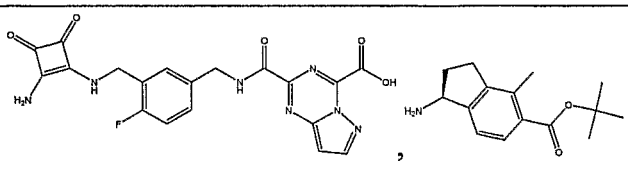
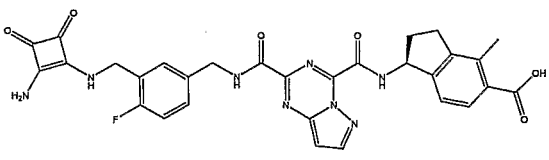
Ex. #	acid, amine	product
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1089		
1090		
1091		
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1093		
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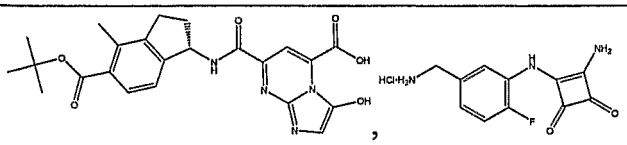
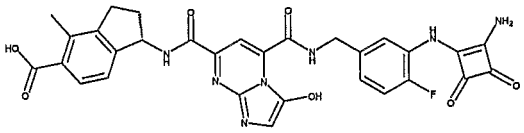
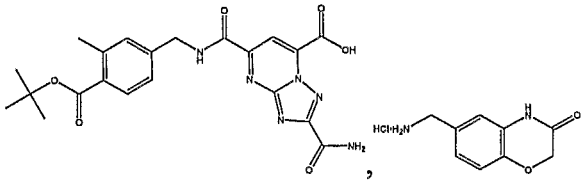
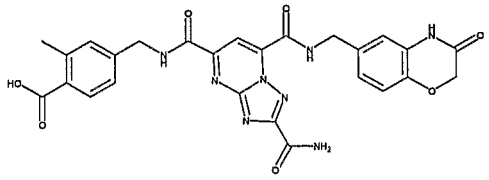
Ex. #	acid, amine	product
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1100		
1101		
1102		
1103		
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1106		
1107		

Ex. #	acid, amine	product
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1109		
1110		
1111		
1112		
1113		
1114		
1115		
1116		
1117		

Ex. #	acid, amine	product
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1119		
1120		
1121		
1122		
1123		
1124		
1125		
1126		
1127		

Ex. #	acid, amine	product
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1129		
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1137		

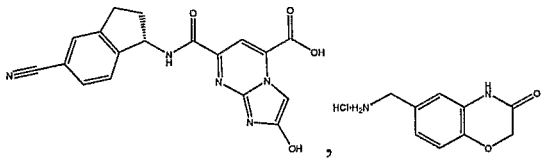
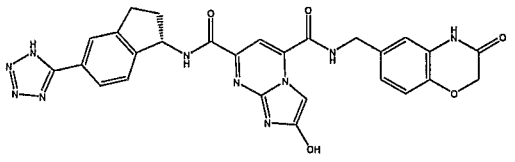
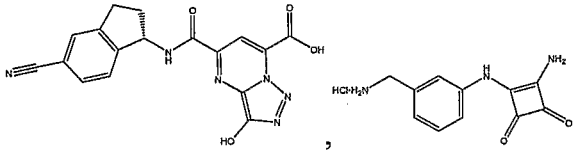
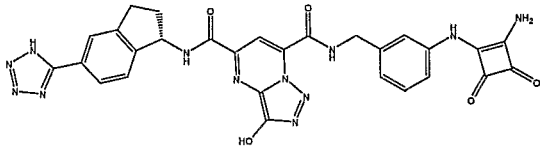
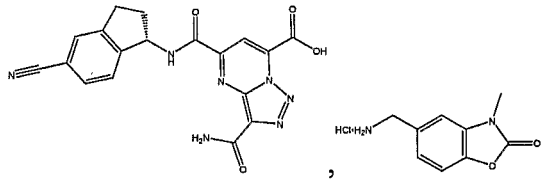
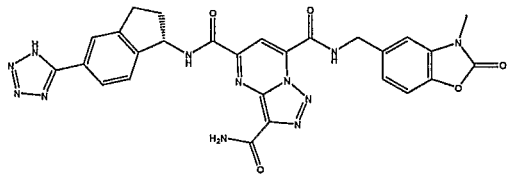
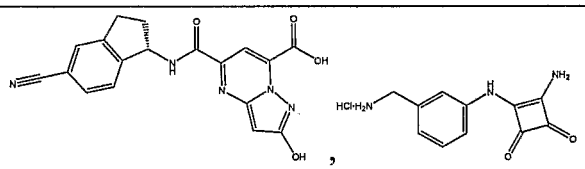
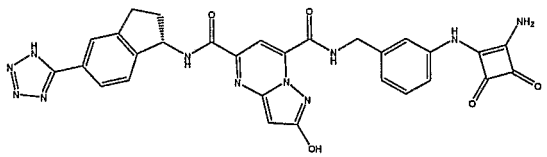
Ex. #	acid, amine	product
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1147		

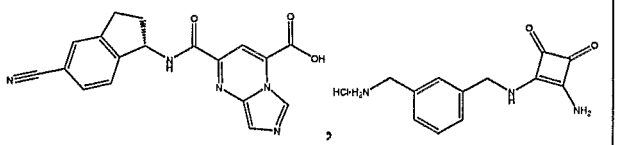
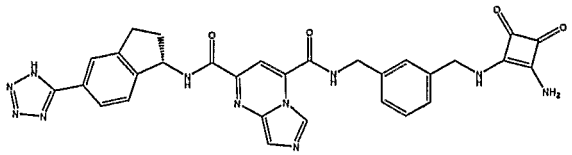
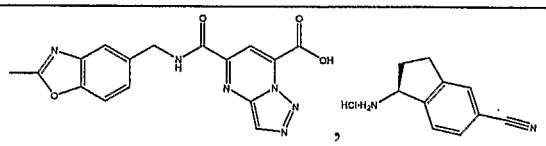
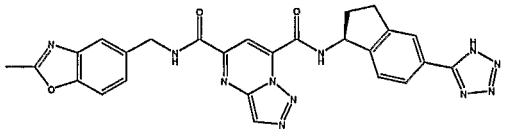
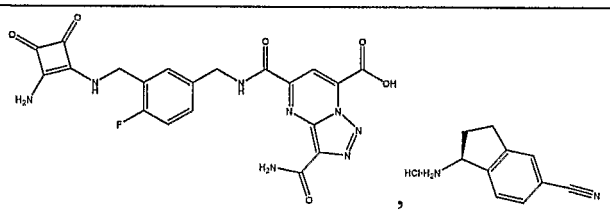
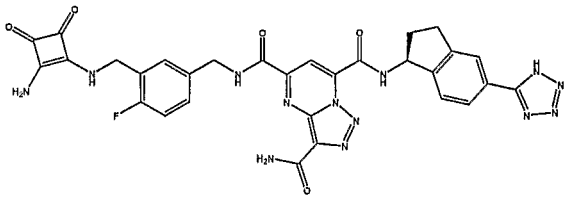
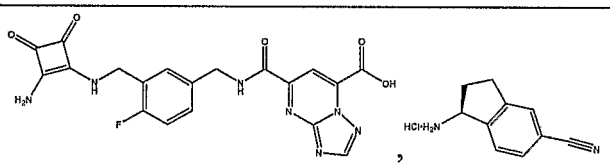
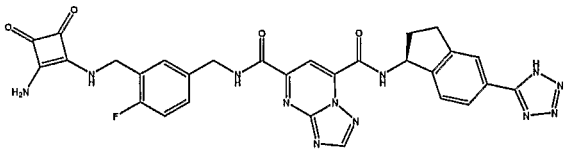
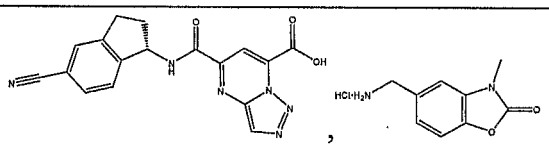
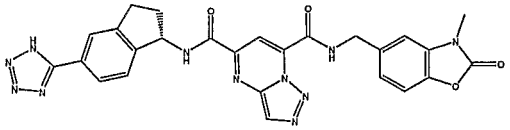
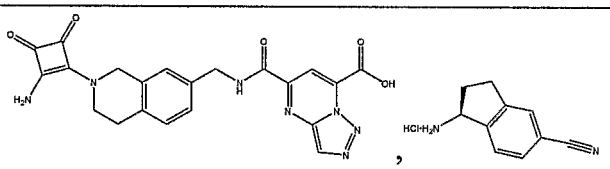
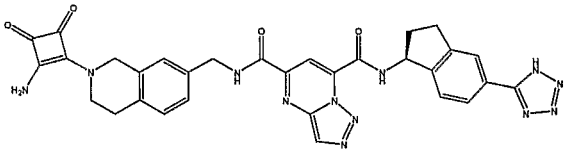
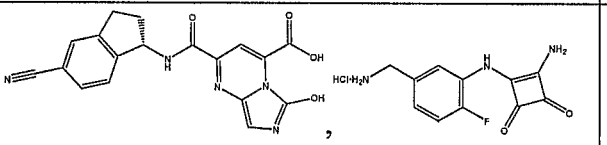
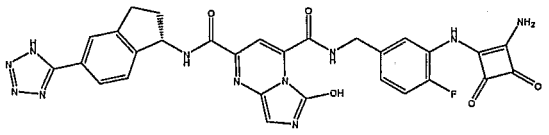
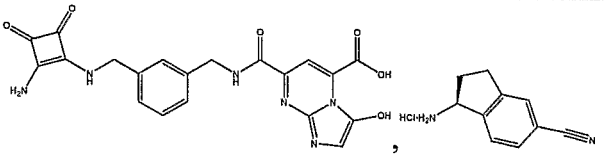
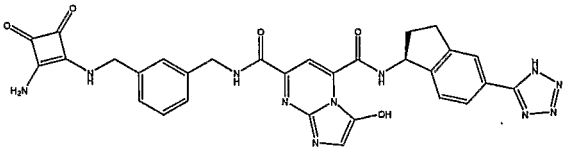
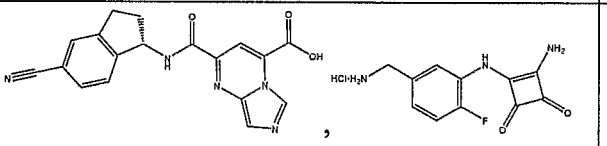
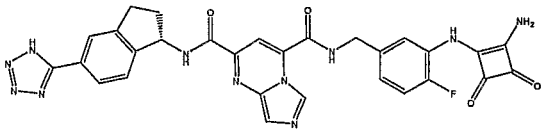
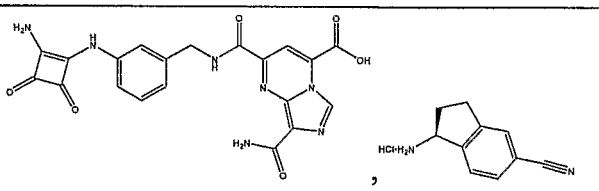
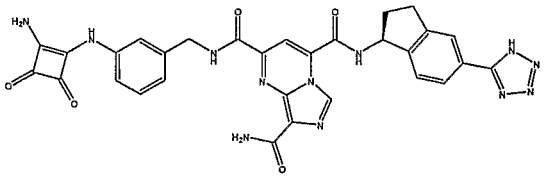
Ex. #	acid, amine	product
1148		
1149		

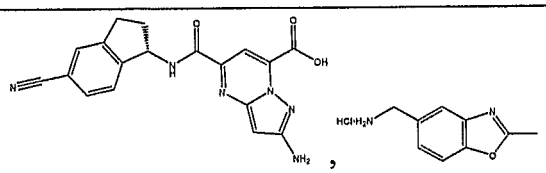
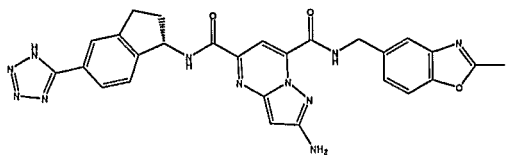
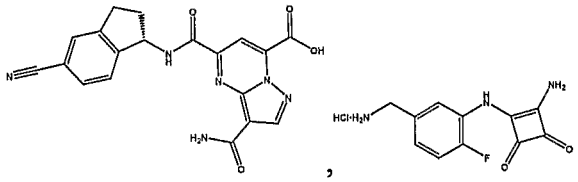
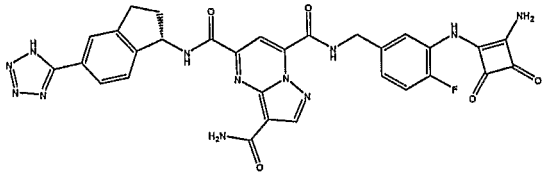
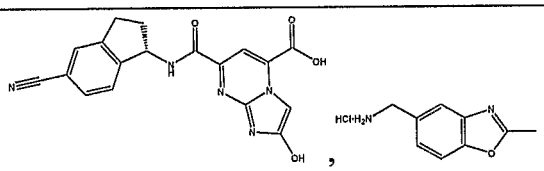
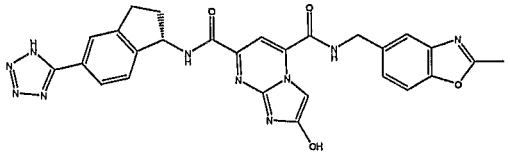
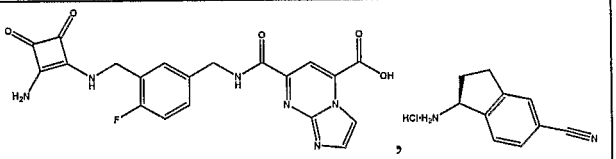
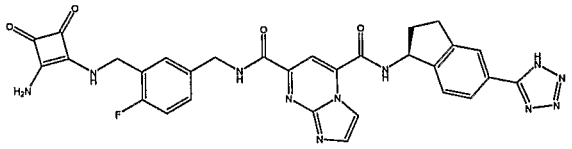
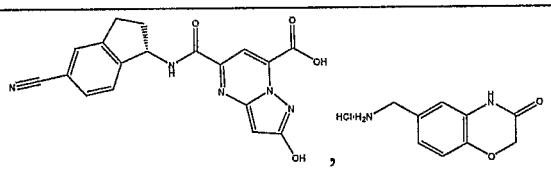
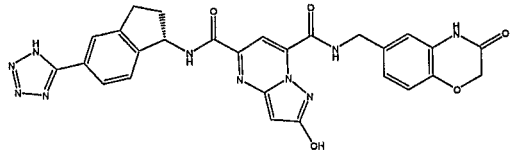
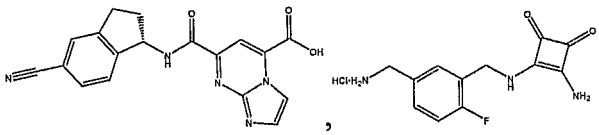
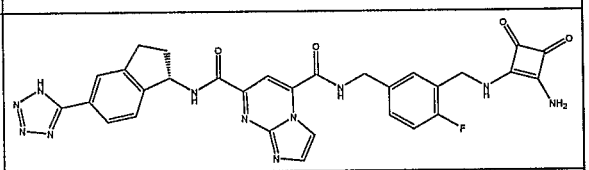
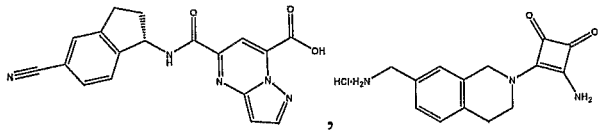
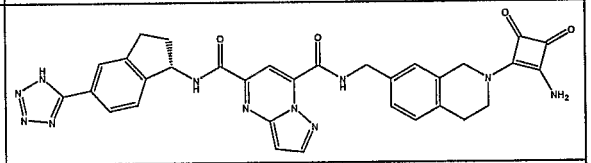
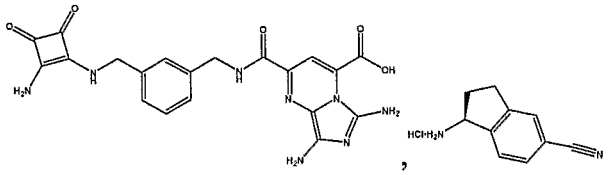
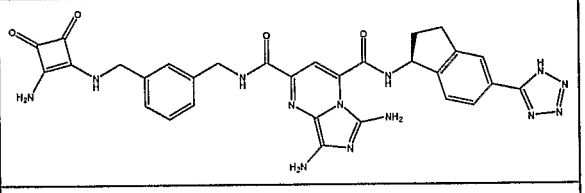
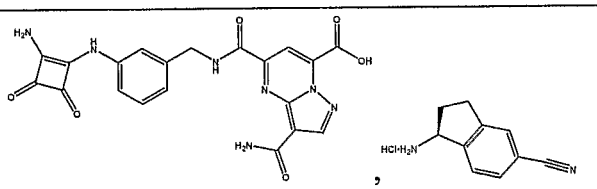
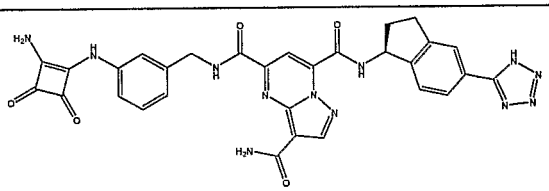
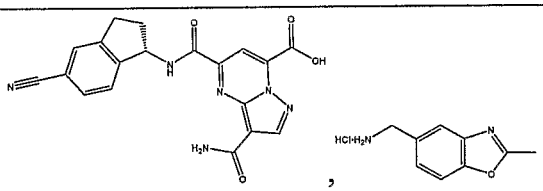
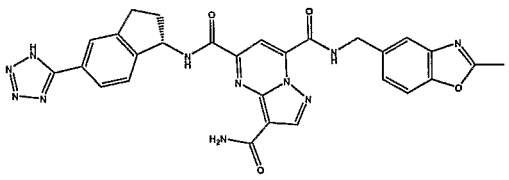
Examples 1150-1229

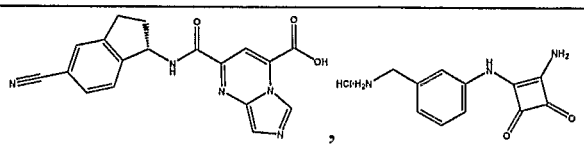
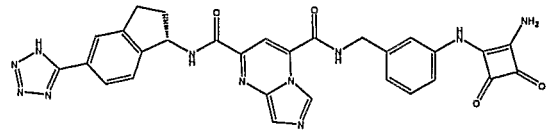
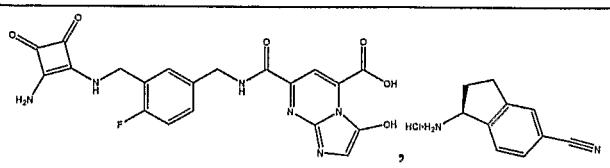
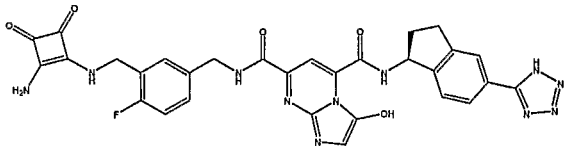
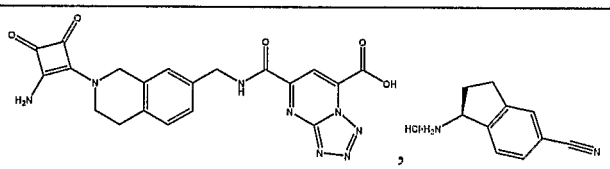
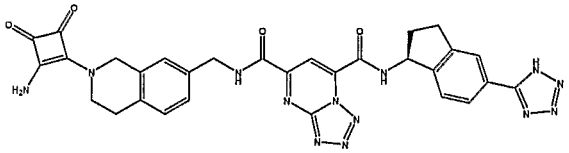
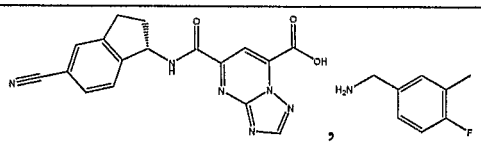
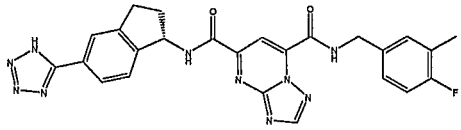
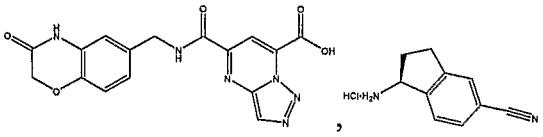
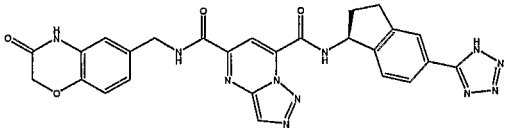
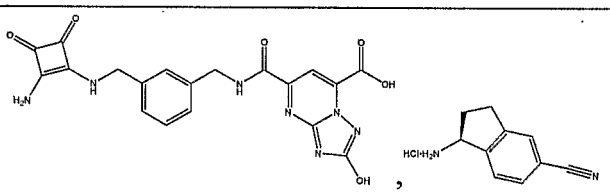
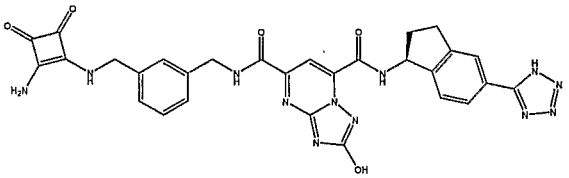
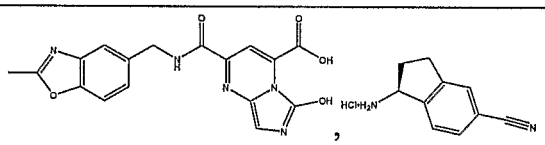
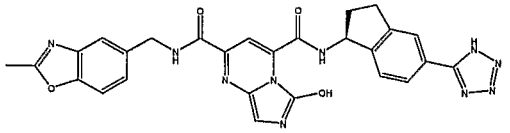
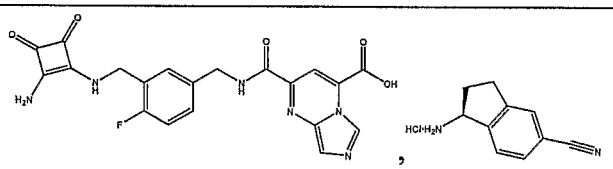
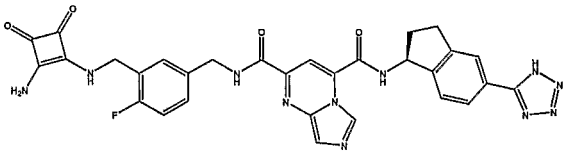
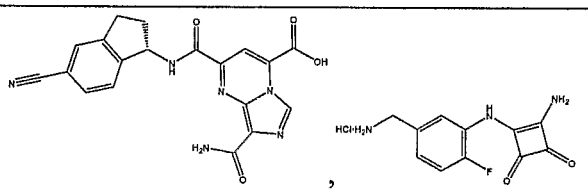
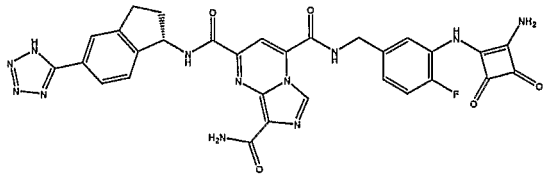
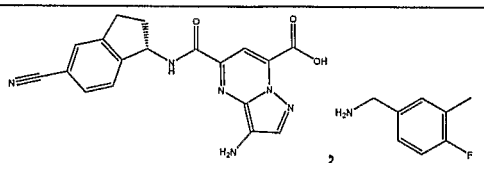
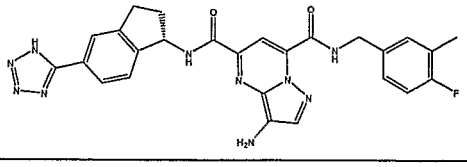
[0595] If one were to follow similar procedures as described in the Examples 1, 2, 3, 4, 5, 6 or 7, except using the acids and amines indicated in Table II-16 below, and if one were to treat the obtained nitriles similarly as described in the Example 469, the following compounds would be obtained.

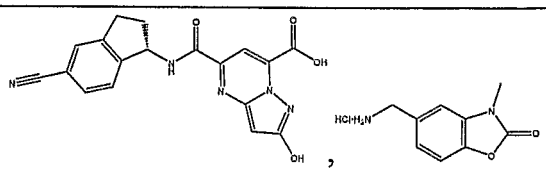
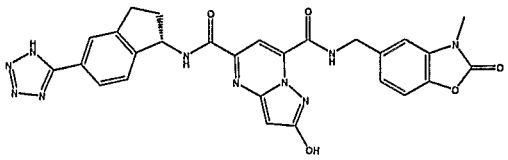
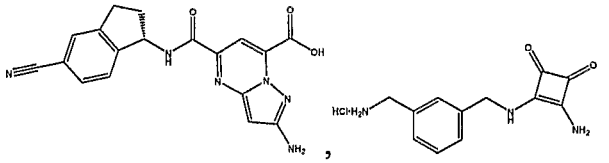
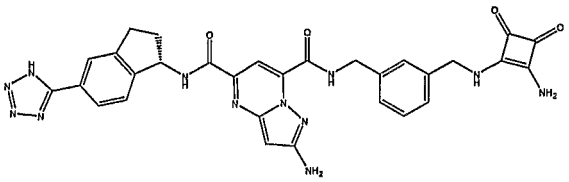
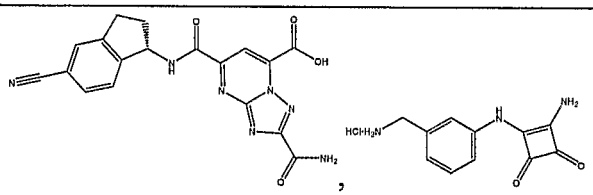
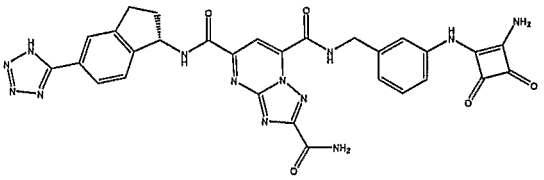
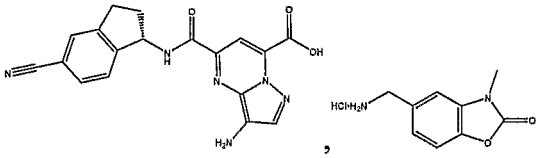
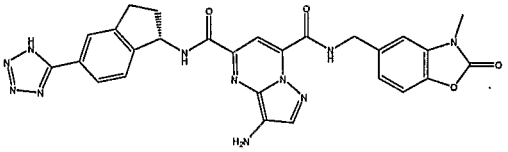
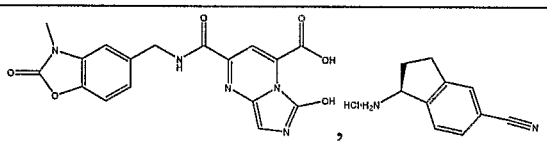
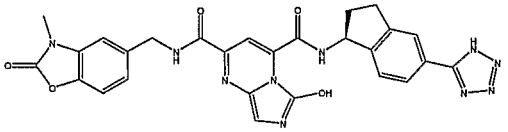
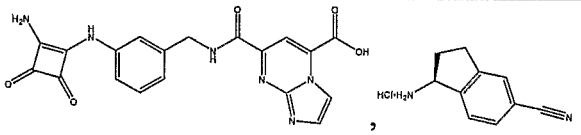
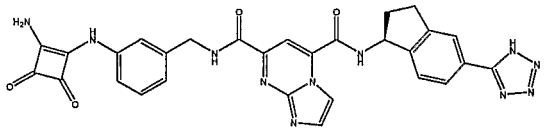
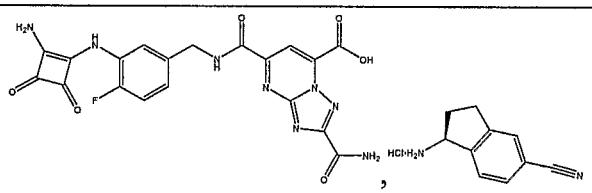
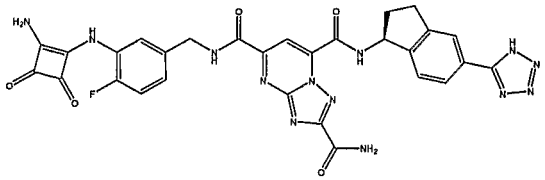
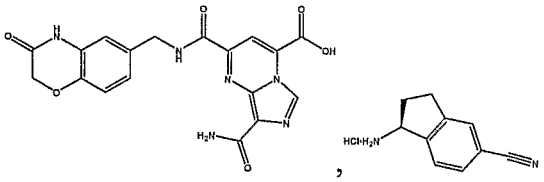
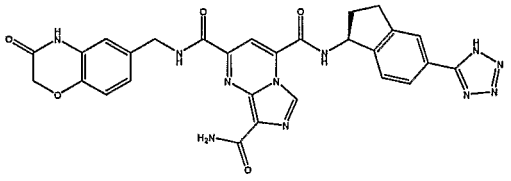
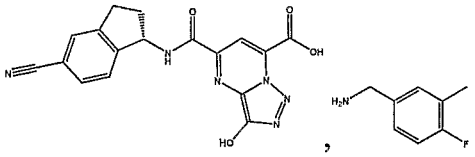
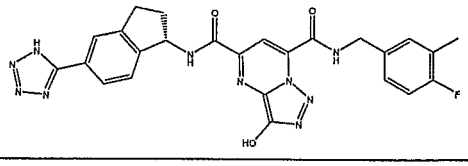
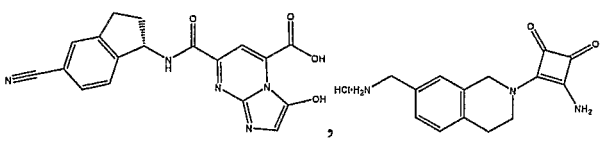
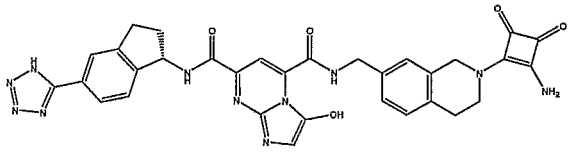
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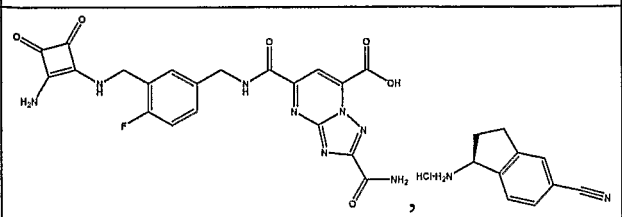
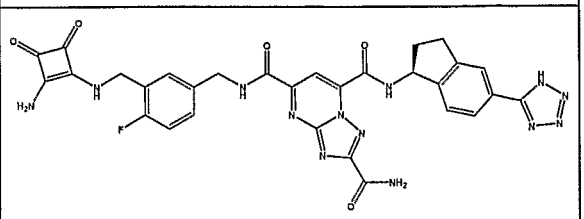
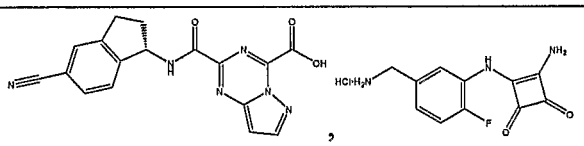
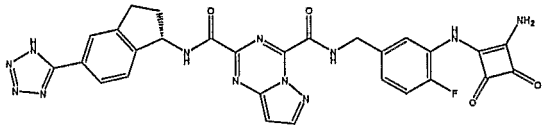
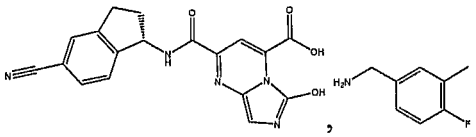
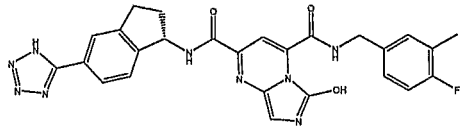
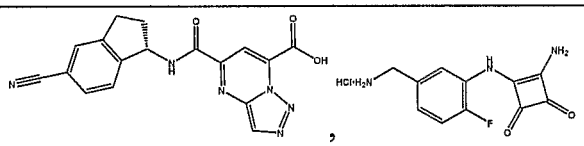
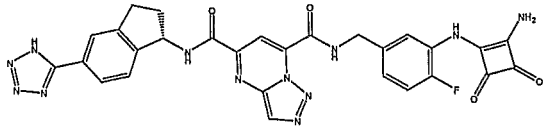
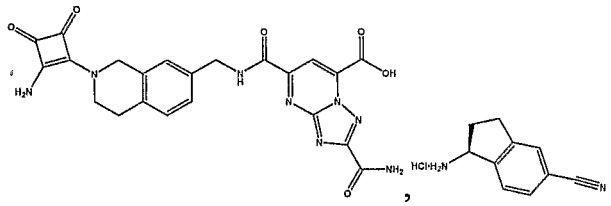
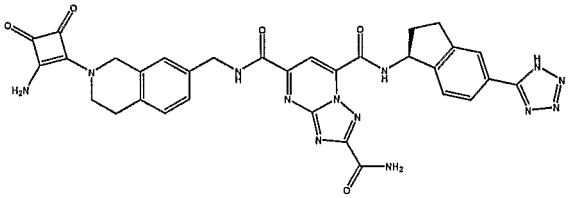
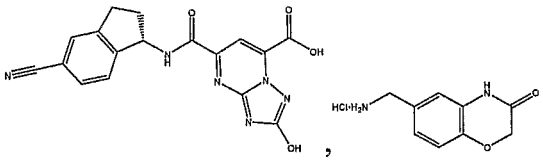
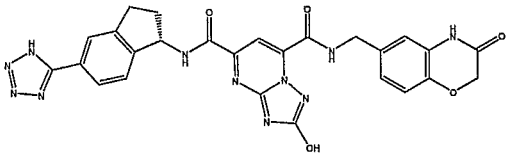
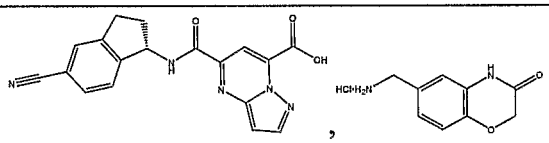
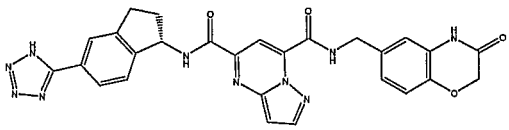
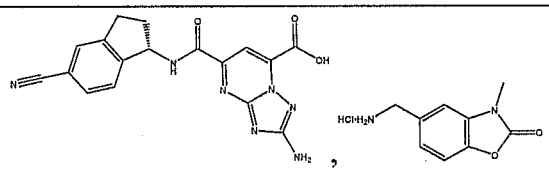
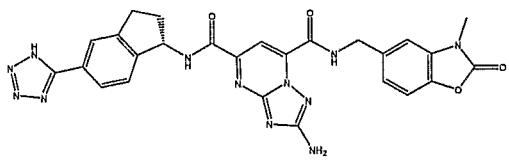
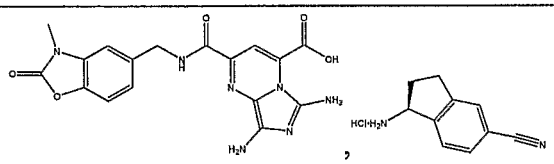
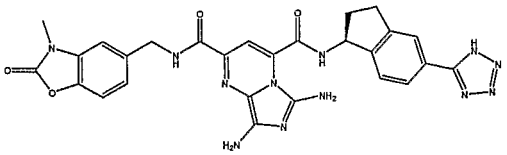
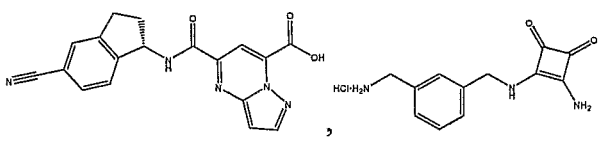
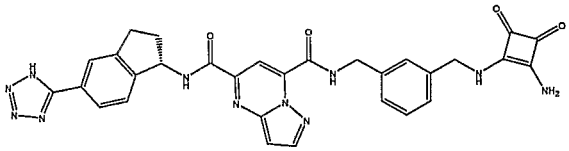
Ex. #	acid, amine	product
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1153		

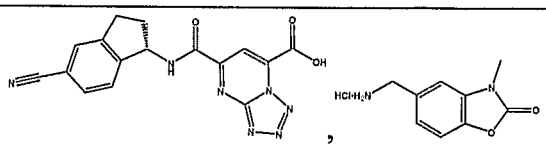
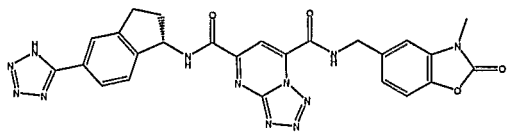
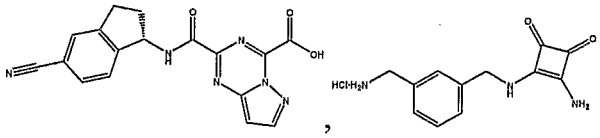
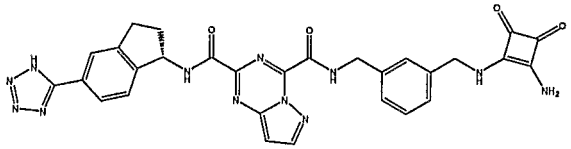
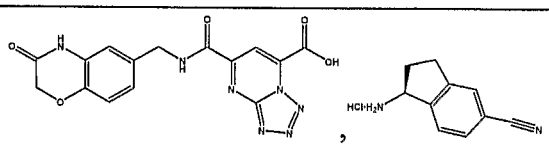
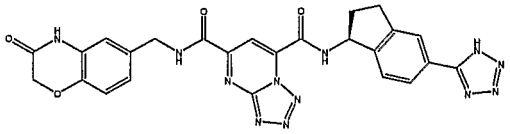
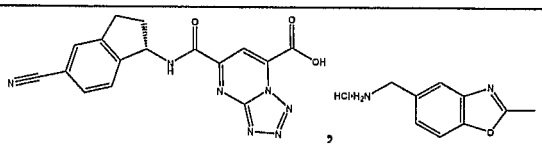
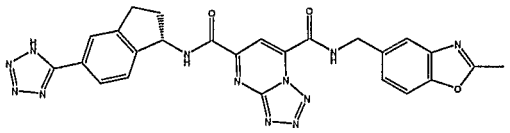
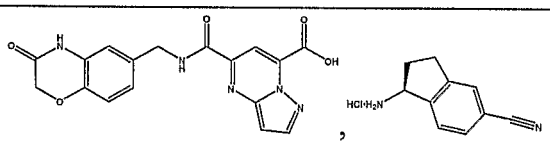
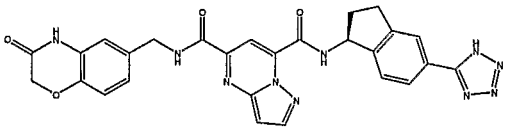
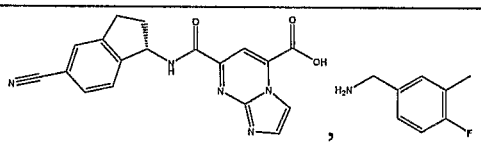
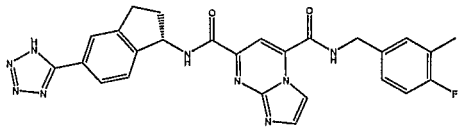
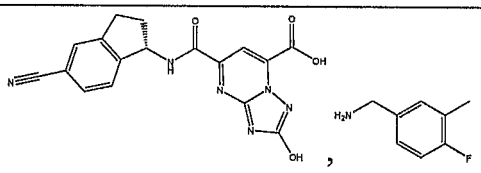
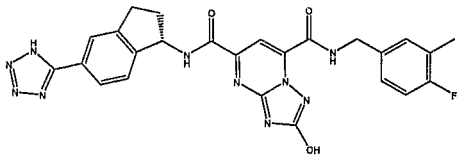
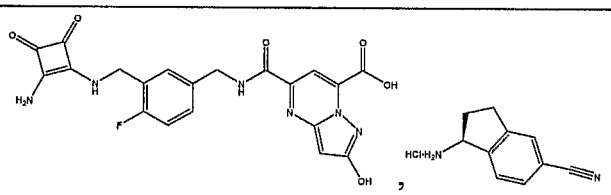
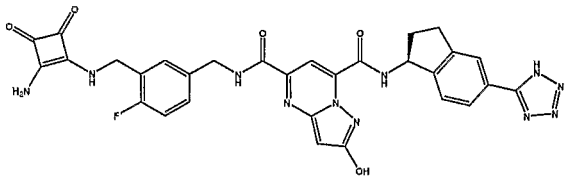
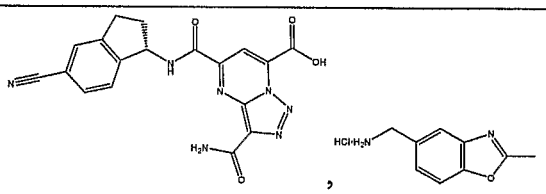
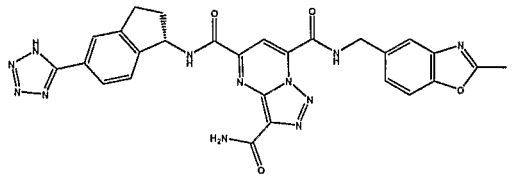
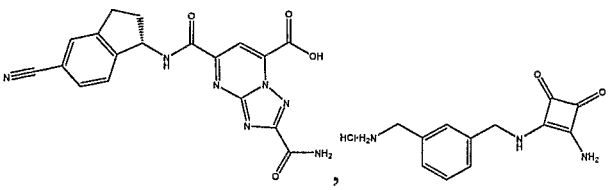
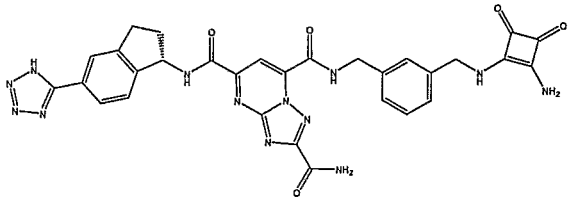
Ex. #	acid, amine	product
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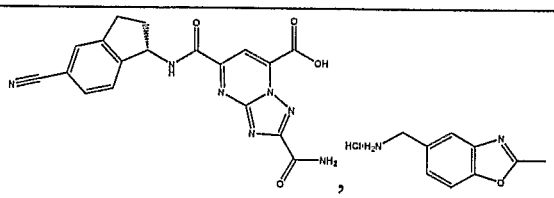
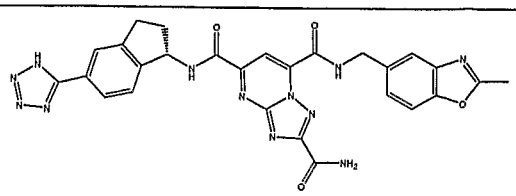
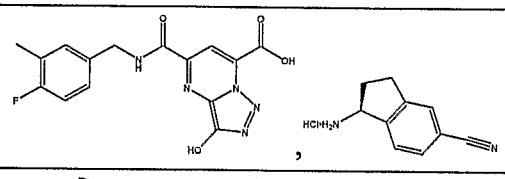
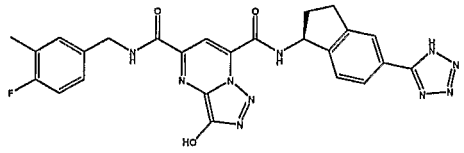
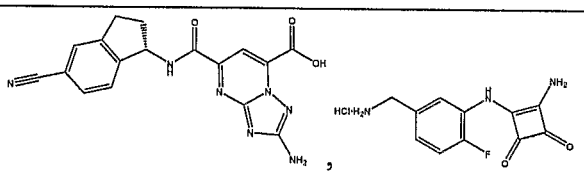
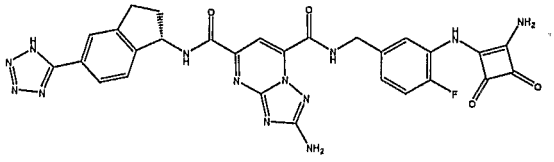
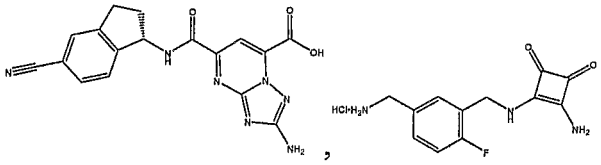
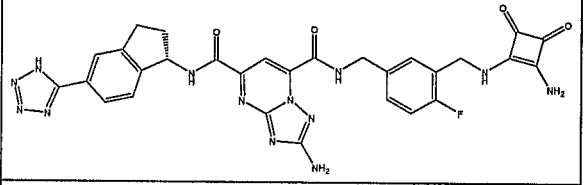
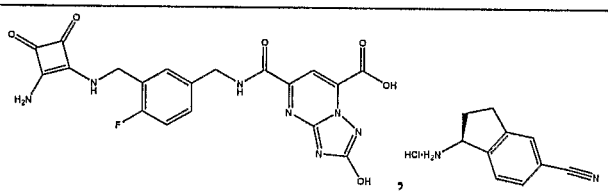
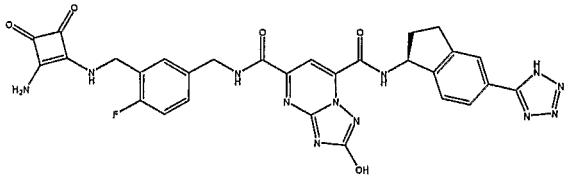
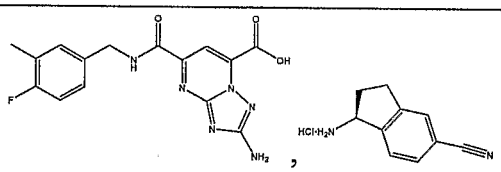
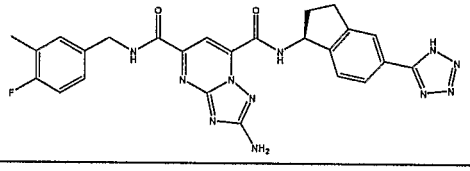
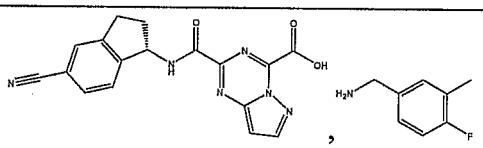
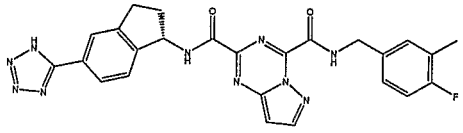
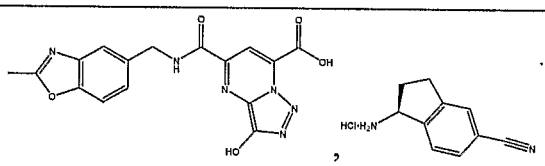
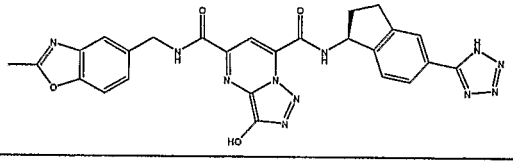
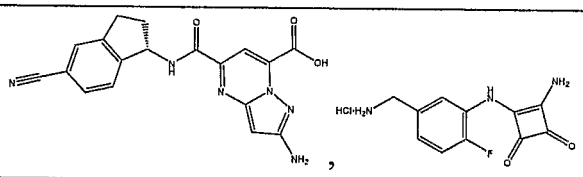
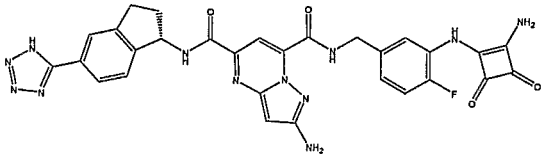
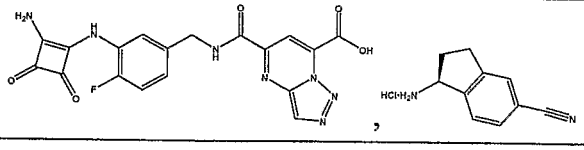
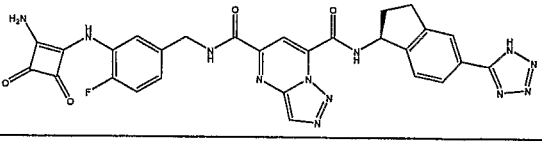
Ex. #	acid, amine	product
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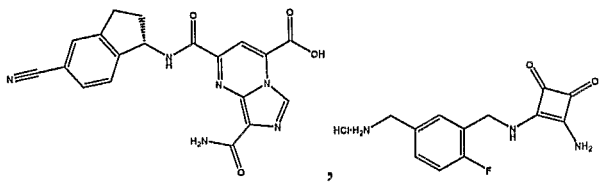
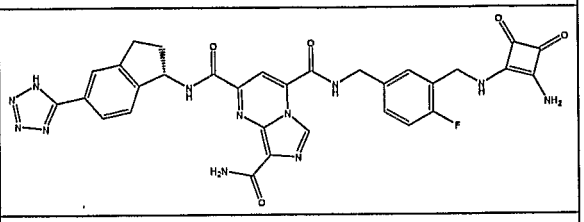
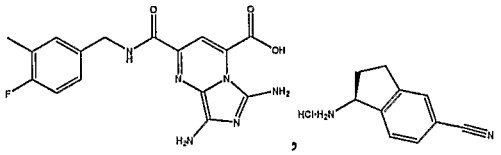
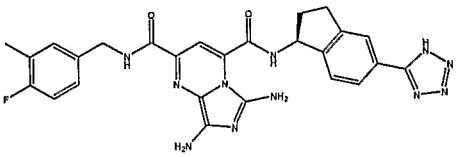
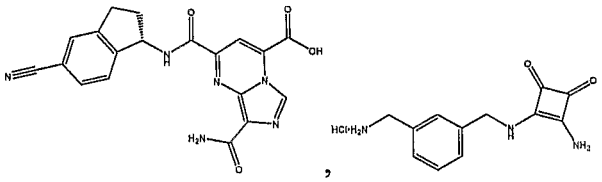
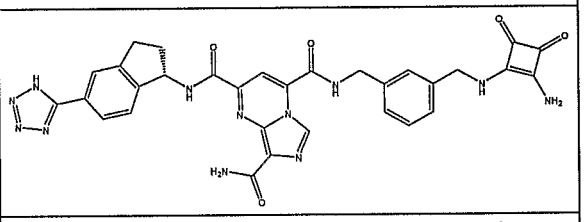
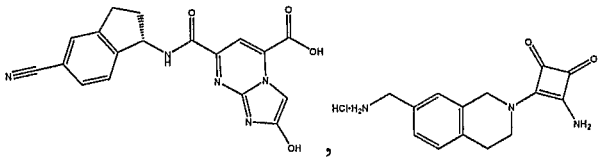
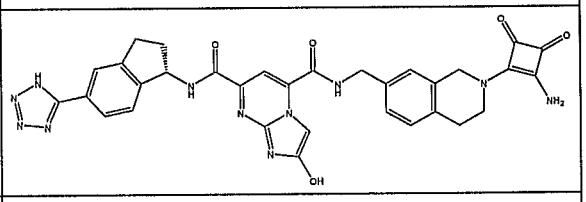
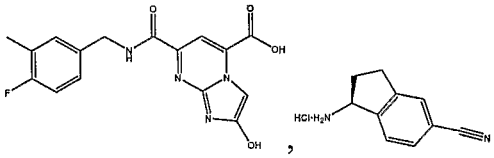
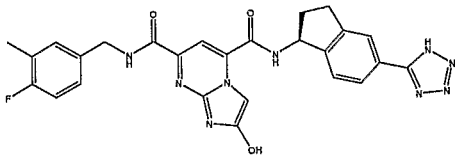
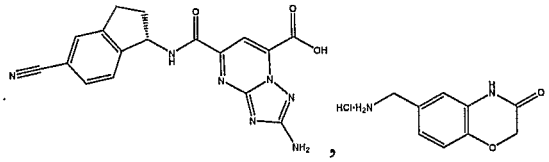
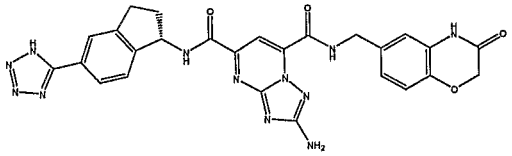
Ex. #	acid, amine	product
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Ex. #	acid, amine	product
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Ex. #	acid, amine	product
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Ex. #	acid, amine	product
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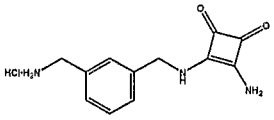
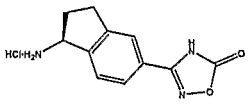
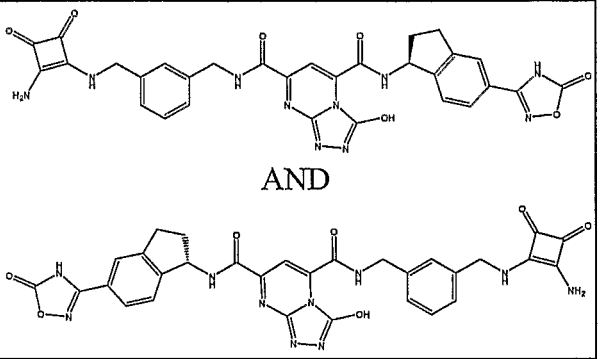
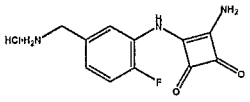
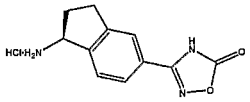
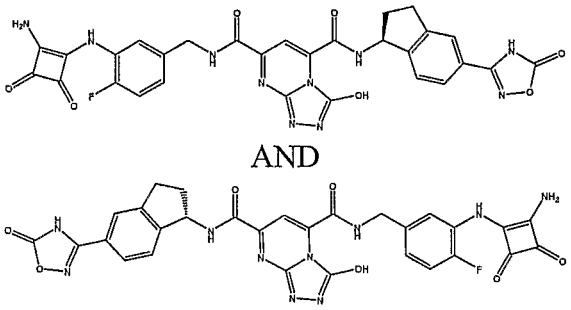
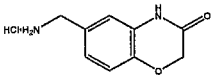
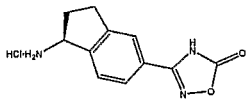
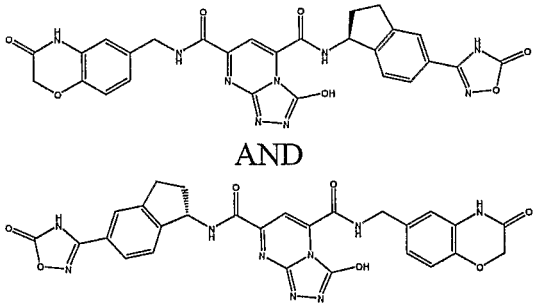
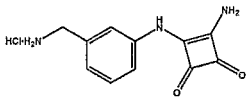
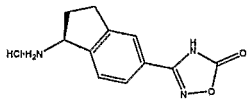
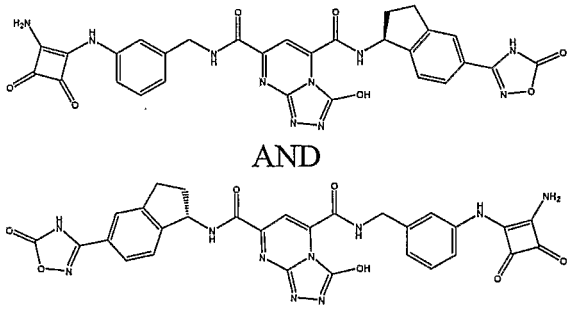
Ex. #	acid, amine	product
1214		
1215		
1216		
1217		
1218		
1219		
1220		
1221		
1222		
1223		

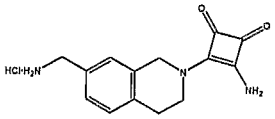
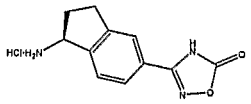
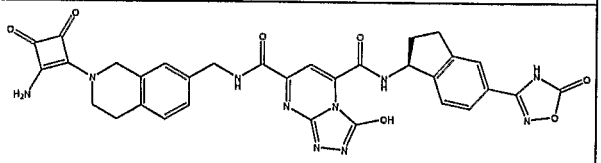
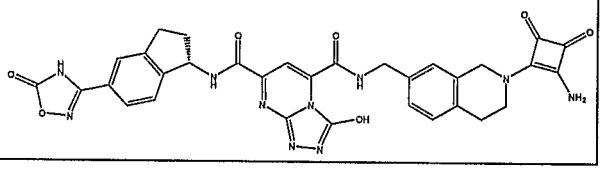
Ex. #	acid, amine	product
1224		
1225		
1226		
1227		
1228		
1229		

Examples 1230-1234

[0596] If one were to follow a similar procedure as described in the Example 295, Step B to Step E, except using the amines indicated in Table II-17 below in Step B and Step D, the following compounds would be obtained.

Table II-17

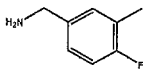
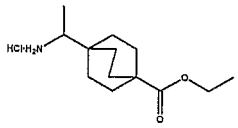
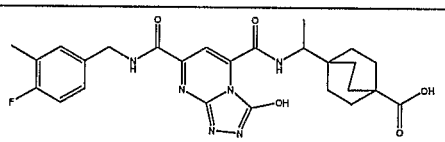
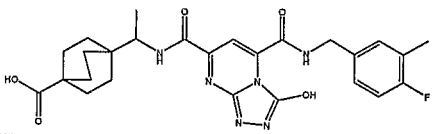
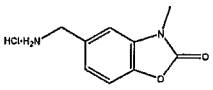
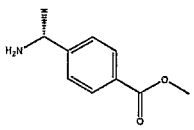
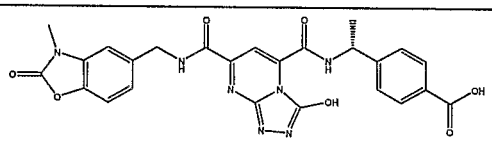
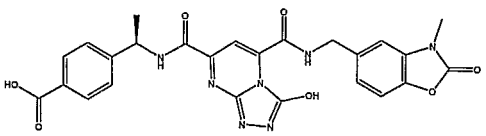
Ex. #	amine (Step B)	amine (Step D)	products
1230			
1231			
1232			
1233			

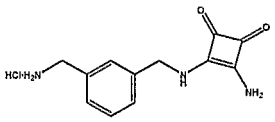
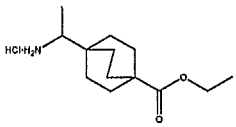
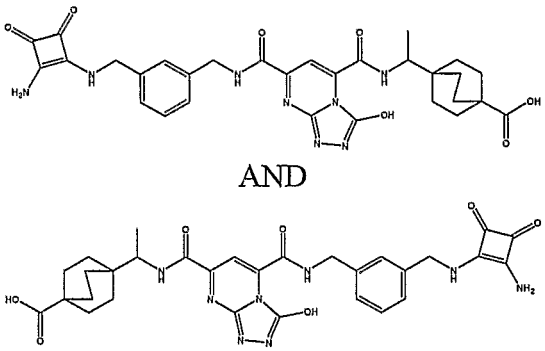
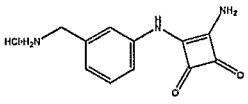
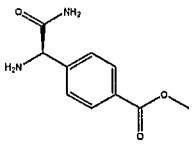
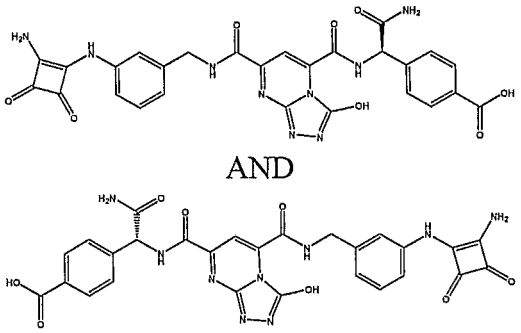
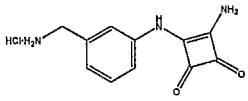
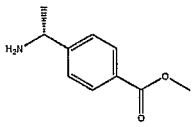
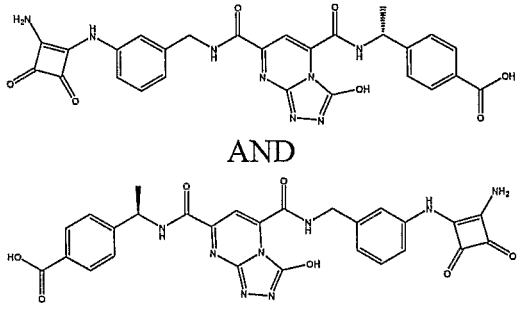
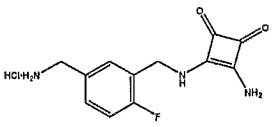
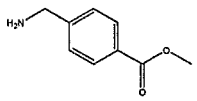
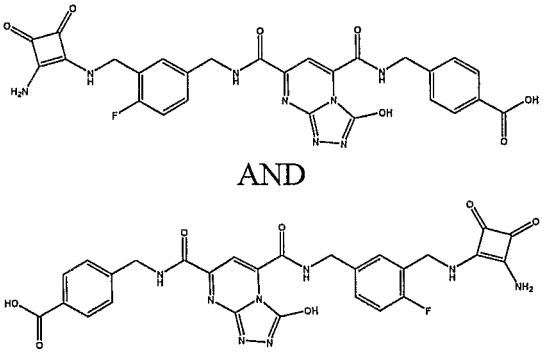
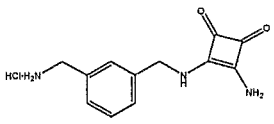
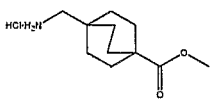
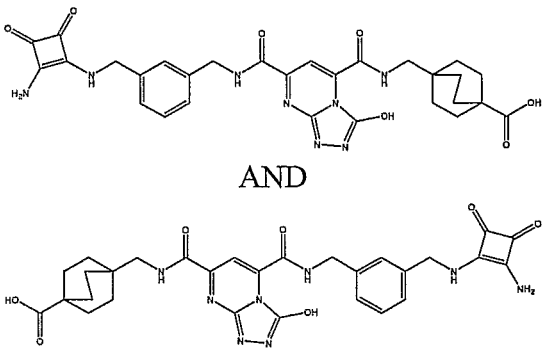
Ex. #	amine (Step B)	amine (Step D)	products
1234			 AND 

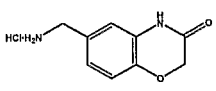
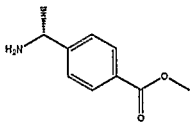
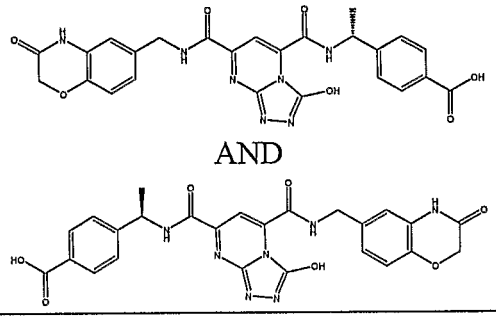
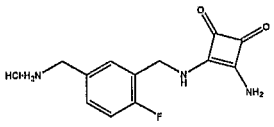
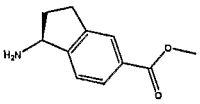
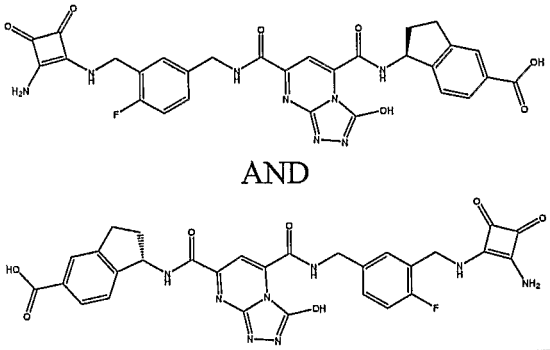
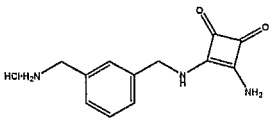
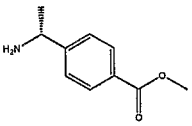
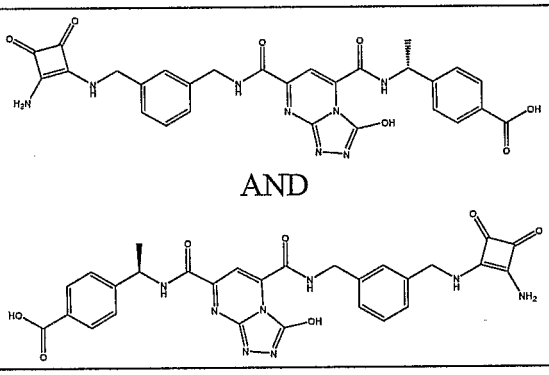
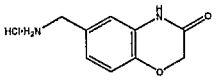
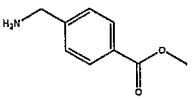
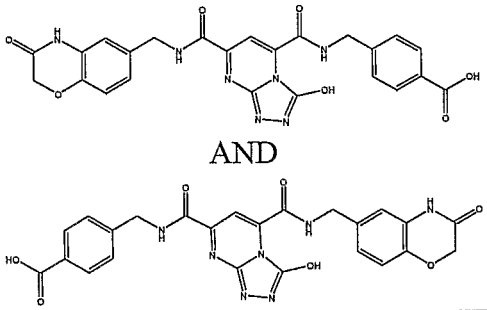
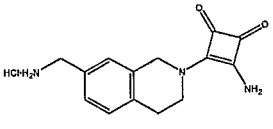
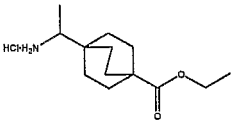
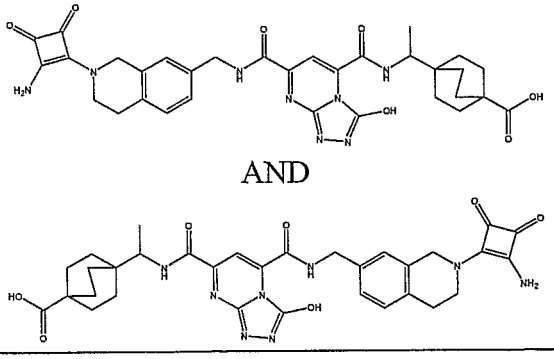
Examples 1235-1254

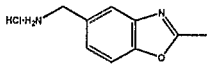
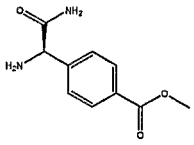
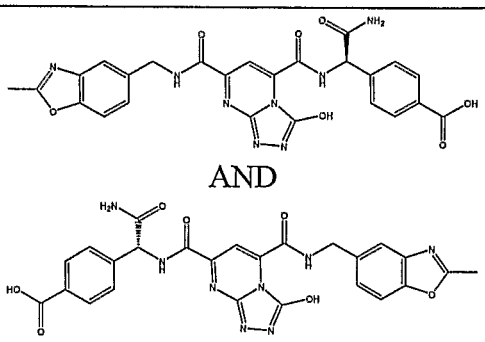
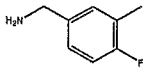
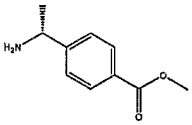
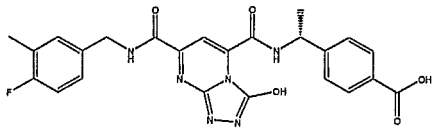
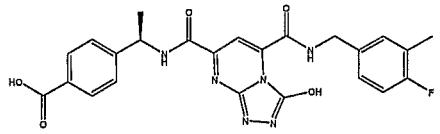
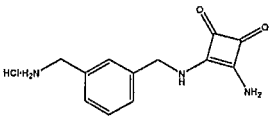
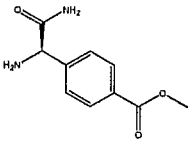
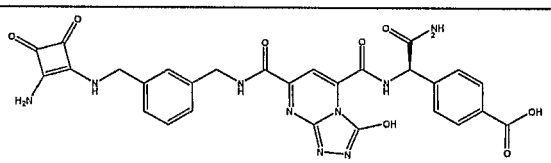
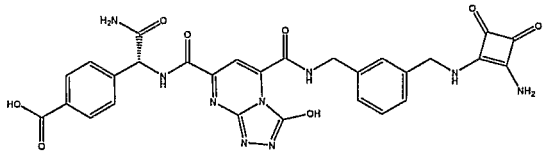
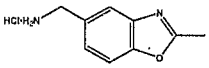
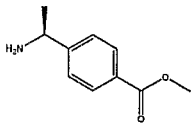
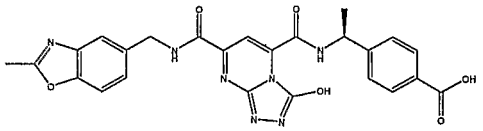
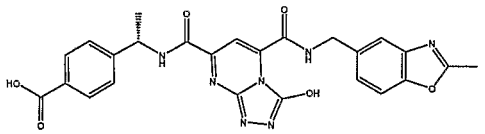
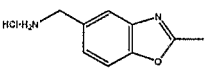
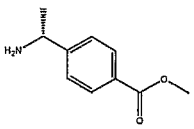
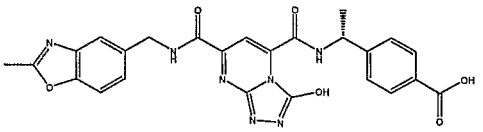
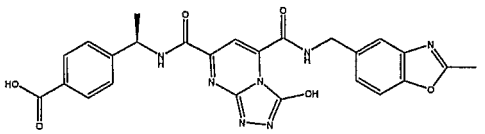
[0597] If one were to follow a similar procedure as described in the Example 295, Step B to Step E, except using the amines indicated in Table II-18 below in Step B and Step D, and if one were to treat the obtained esters similarly as described in the Examples 314 or 315, the following compounds would be obtained.

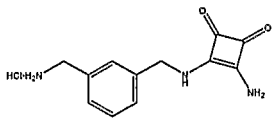
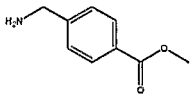
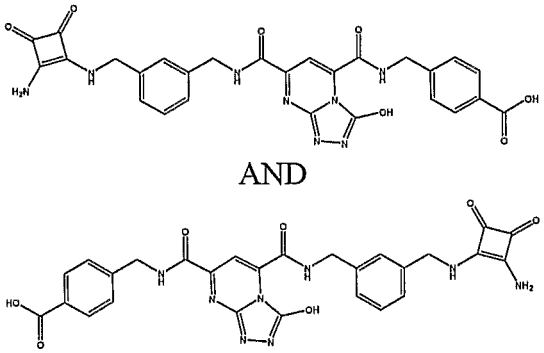
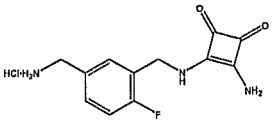
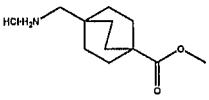
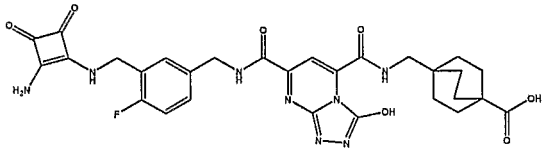
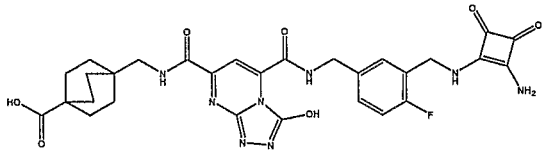
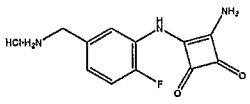
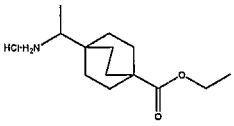
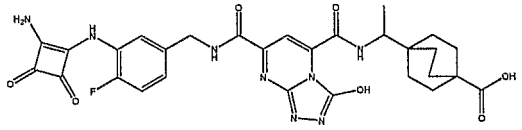
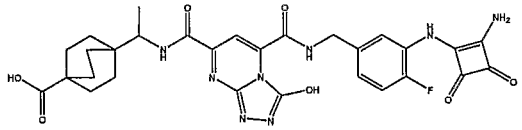
Table II-18

Ex. #	amine (Step B)	amine (Step D)	products
1235			 AND 
1236			 AND 

Ex. #	amine (Step B)	amine (Step D)	products
1237			
1238			
1239			
1240			
1241			

Ex. #	amine (Step B)	amine (Step D)	products
1242			
1243			
1244			
1245			
1246			

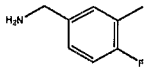
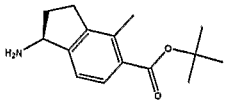
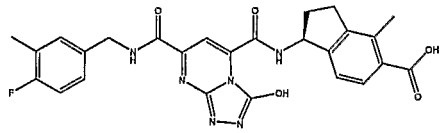
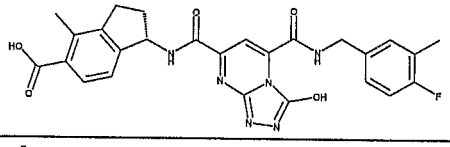
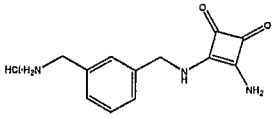
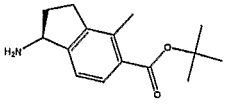
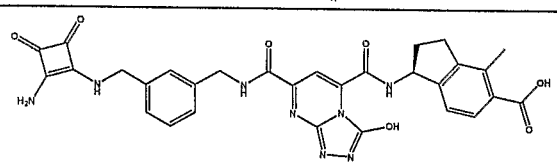
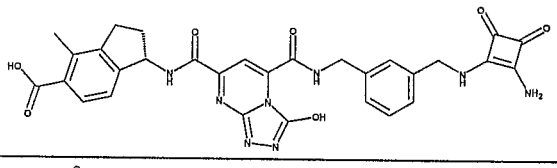
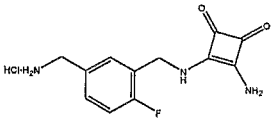
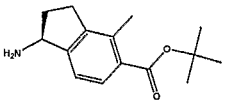
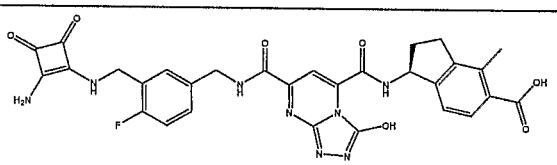
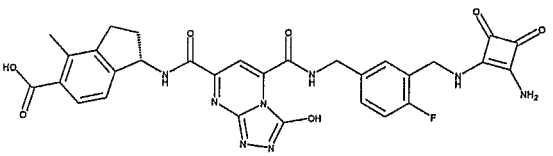
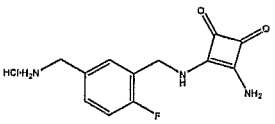
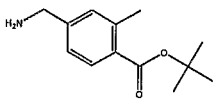
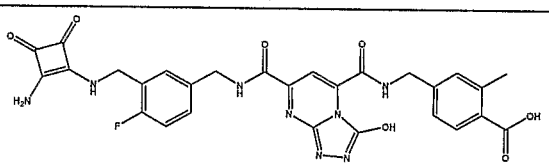
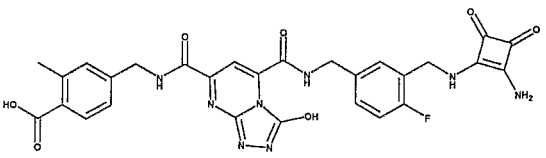
Ex. #	amine (Step B)	amine (Step D)	products
1247			 AND
1248			 AND 
1249			 AND 
1250			 AND 
1251			 AND 

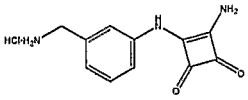
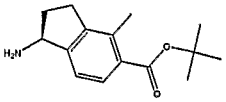
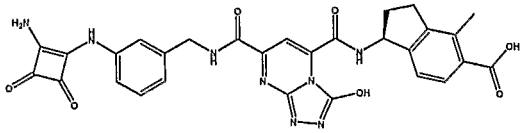
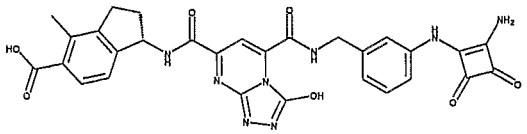
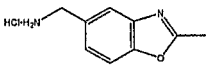
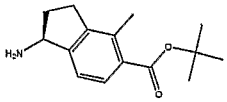
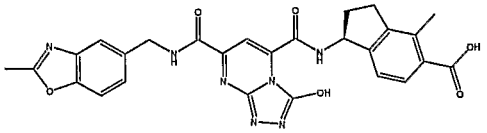
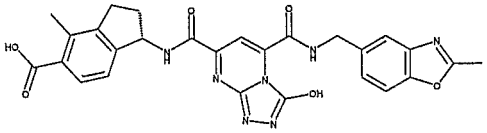
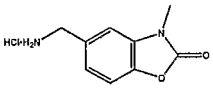
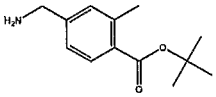
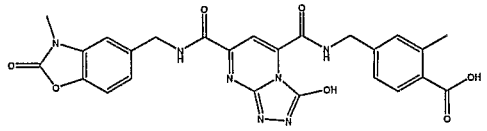
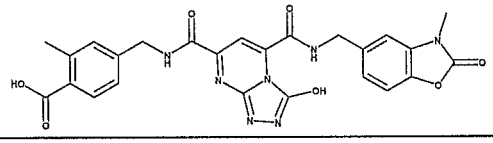
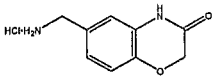
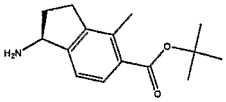
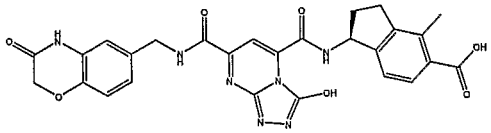
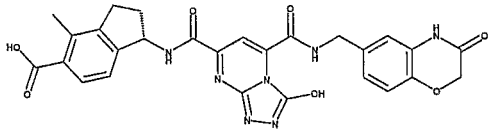
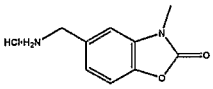
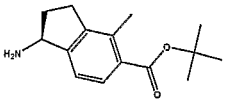
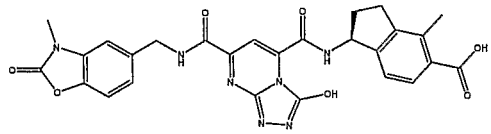
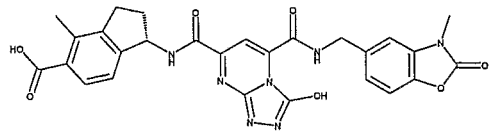
Ex. #	amine (Step B)	amine (Step D)	products
1252			 AND
1253			 AND 
1254			 AND 

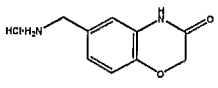
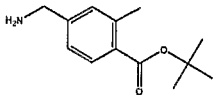
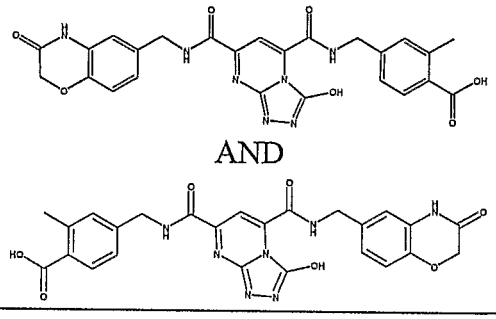
Examples 1255-1264

[0598] If one were to follow a similar procedure as described in the Example 295, Step B to Step E, except using the amines indicated in Table II-19 below in Step B and Step D, and if one were to treat the obtained esters similarly as described in the Example 436, the following compounds would be obtained.

Table II-19

Ex. #	amine (Step B)	amine (Step D)	products
1255			 AND 
1256			 AND 
1257			 AND 
1258			 AND 

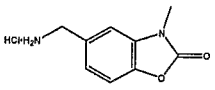
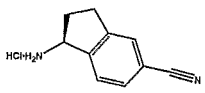
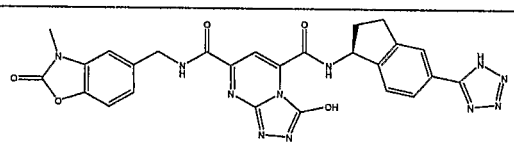
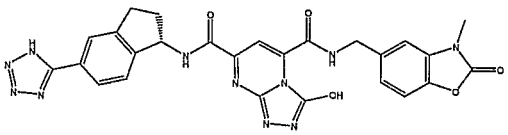
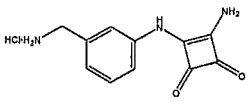
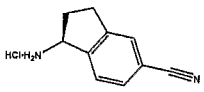
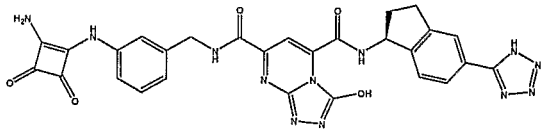
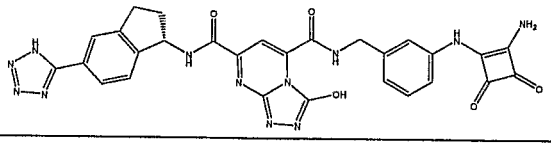
Ex. #	amine (Step B)	amine (Step D)	products
1259			 AND 
1260			 AND 
1261			 AND 
1262			 AND 
1263			 AND 

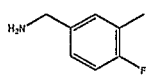
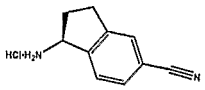
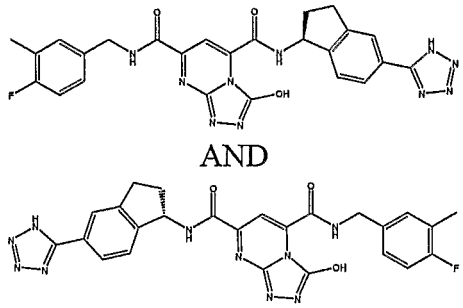
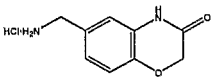
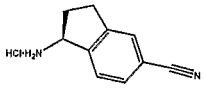
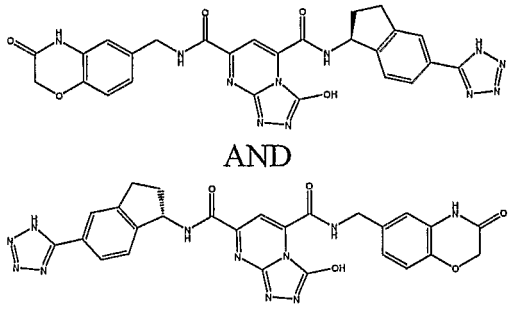
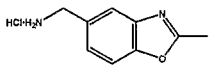
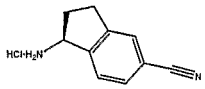
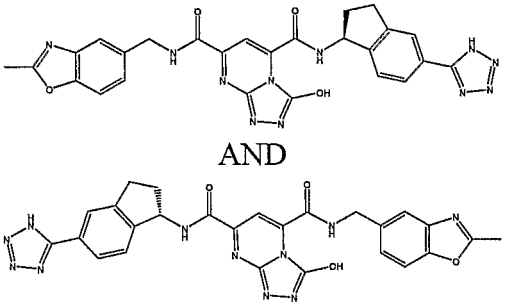
Ex. #	amine (Step B)	amine (Step D)	products
1264			 AND

Examples 1265-1269

[0599] If one were to follow a similar procedure as described in the Example 295, Step B to Step E, except using the amines indicated in Table II-20 below in Step B and Step D, and if one were to treat the obtained nitriles similarly as described in the Example 469, the following compounds would be obtained.

Table II-20

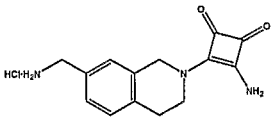
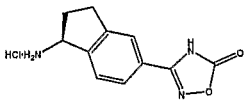
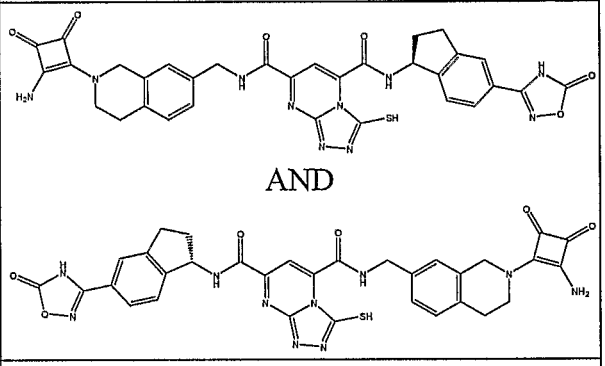
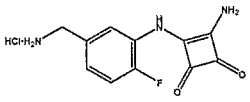
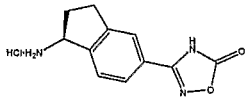
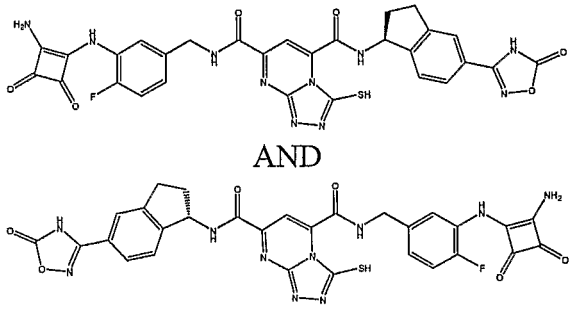
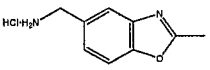
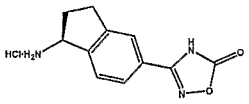
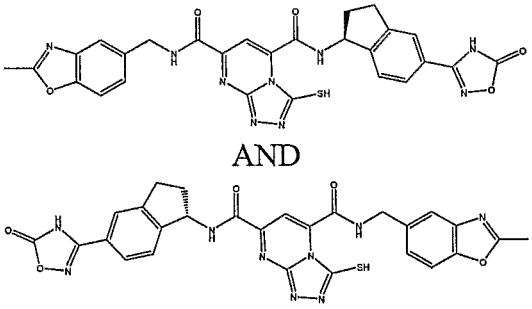
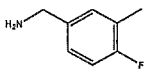
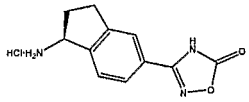
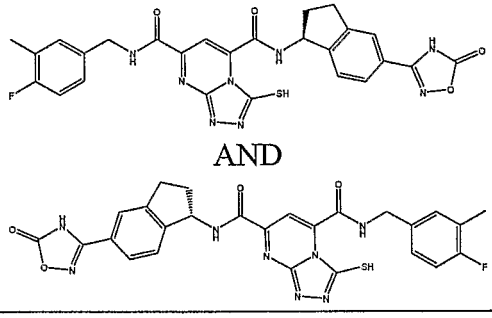
Ex. #	amine (Step B)	amine (Step D)	products
1265			 AND 
1266			 AND 

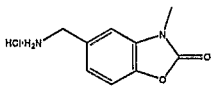
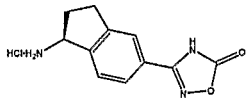
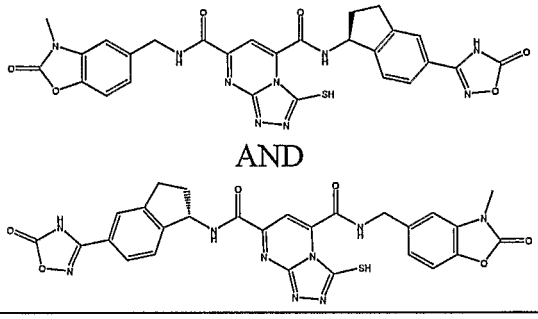
Ex. #	amine (Step B)	amine (Step D)	products
1267			
1268			
1269			

Examples 1270-1274

[0600] If one were to follow a similar procedure as described in the Example 295, Step B to Step E, except using the amines indicated in Table II-21 below in Step B and Step D and thiophosgene instead of phosgene in Step E, the following compounds would be obtained.

Table II-21

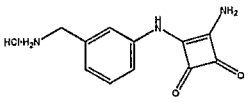
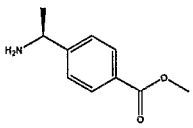
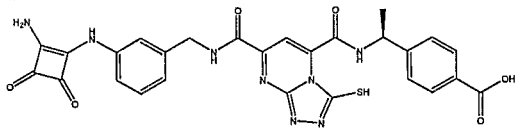
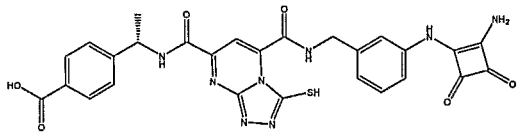
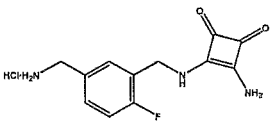
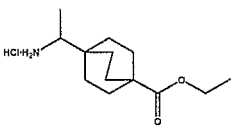
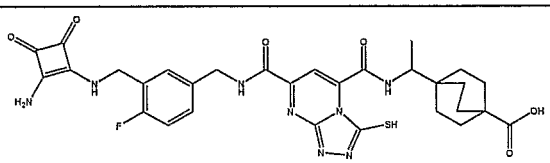
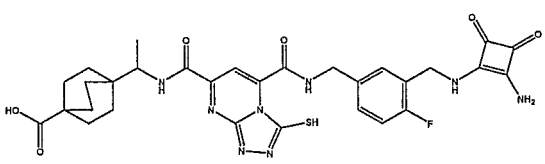
Ex. #	amine (Step B)	amine (Step D)	products
1270			
1271			
1272			
1273			

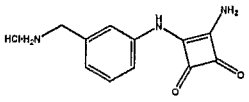
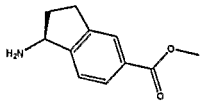
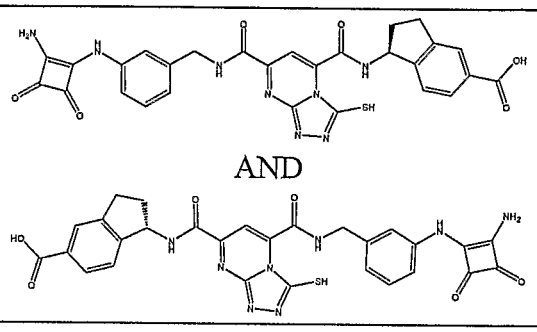
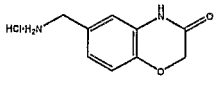
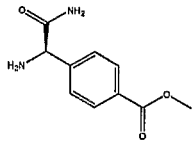
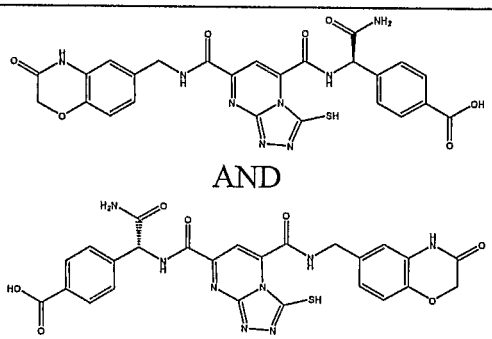
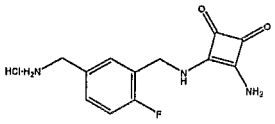
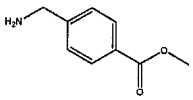
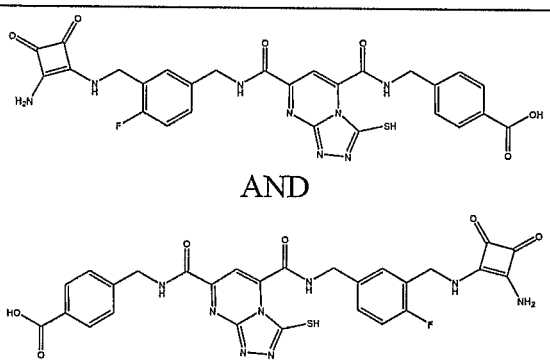
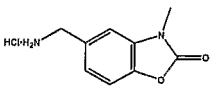
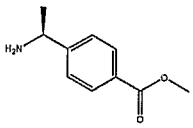
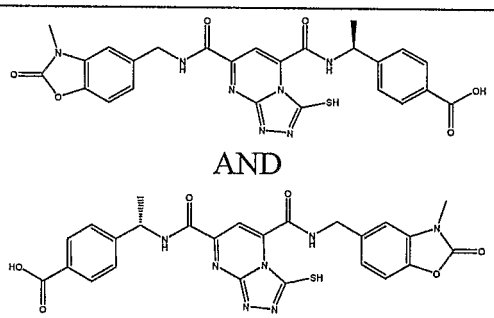
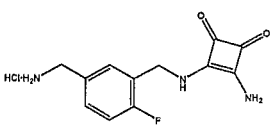
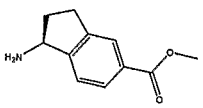
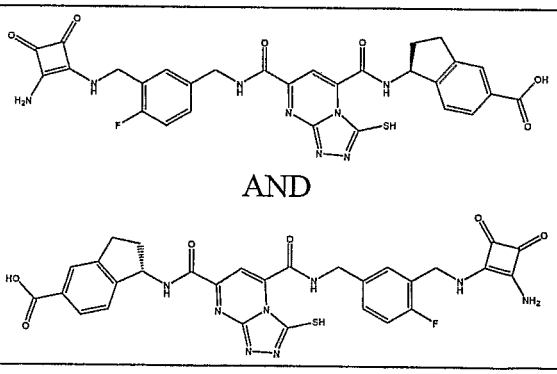
Ex. #	amine (Step B)	amine (Step D)	products
1274			 AND

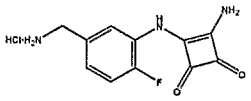
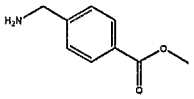
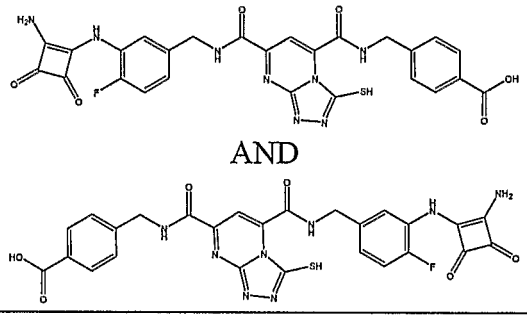
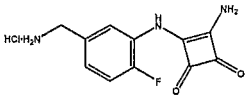
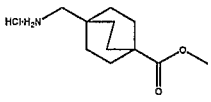
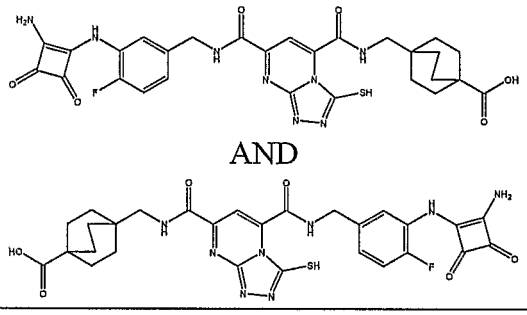
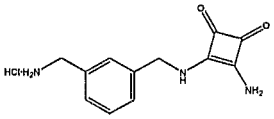
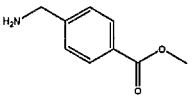
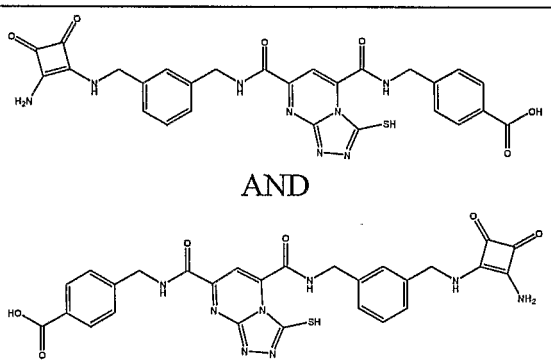
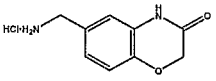
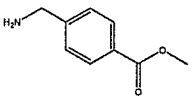
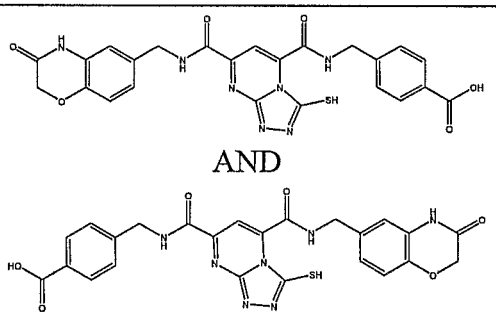
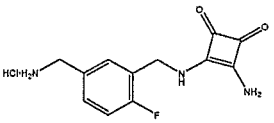
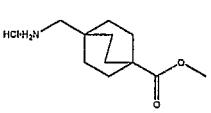
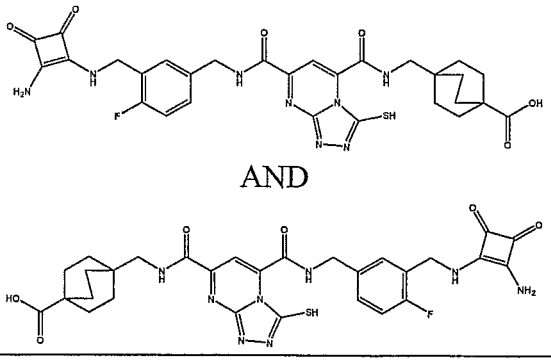
Examples 1275-1294

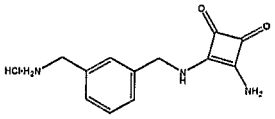
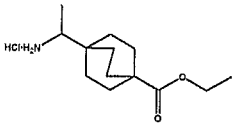
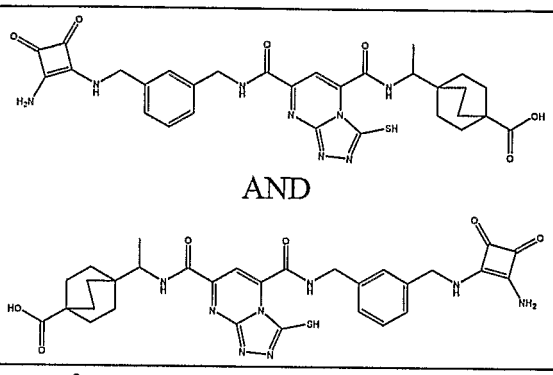
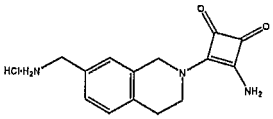
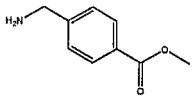
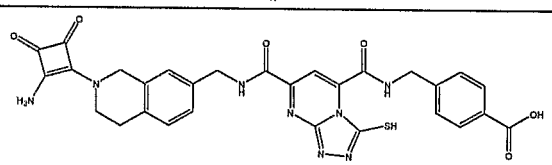
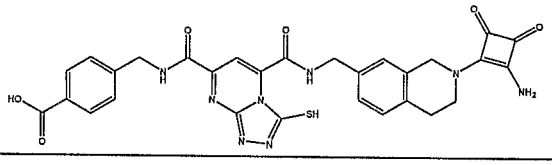
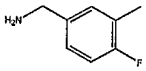
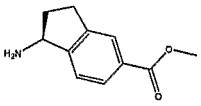
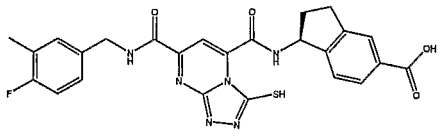
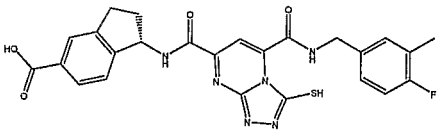
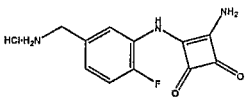
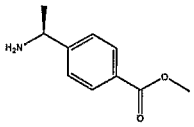
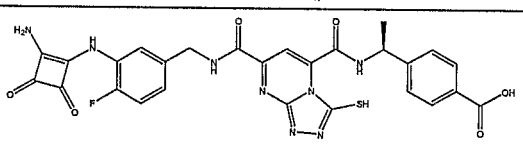
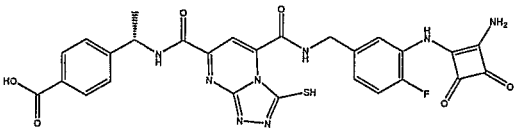
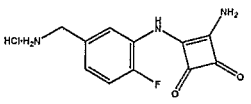
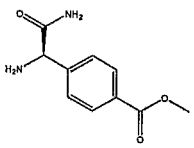
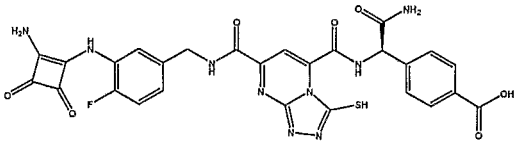
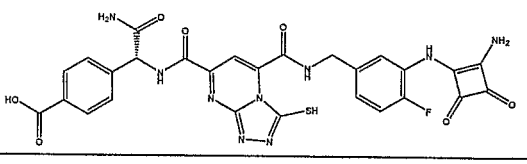
[0601] If one were to follow a similar procedure as described in the Example 295, Step B to Step E, except using the amines indicated in Table II-22 below in Step B and Step D and thiophosgene instead of phosgene in Step E, and if one were to treat the obtained esters similarly as described in the Examples 314 or 315, the following compounds would be obtained.

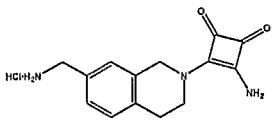
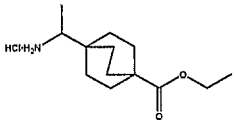
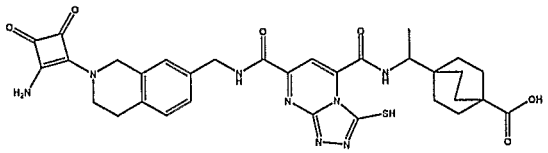
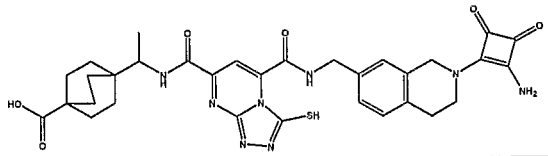
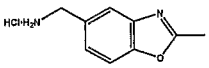
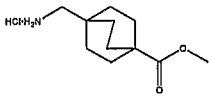
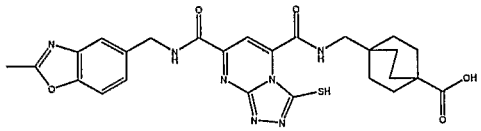
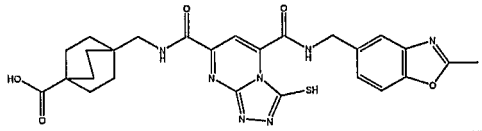
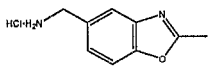
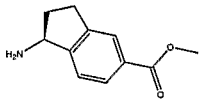
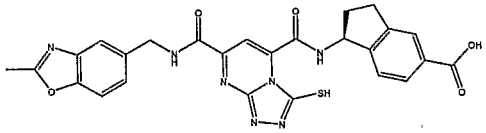
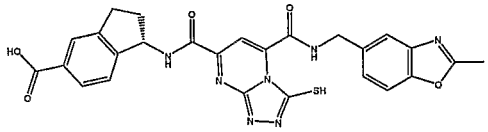
Table II-22

Ex. #	amine (Step B)	amine (Step D)	products
1275			 AND 
1276			 AND 

Ex. #	amine (Step B)	amine (Step D)	products
1277			
1278			
1279			
1280			
1281			

Ex. #	amine (Step B)	amine (Step D)	products
1282			
1283			
1284			
1285			
1286			

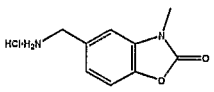
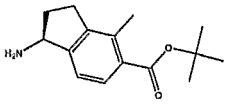
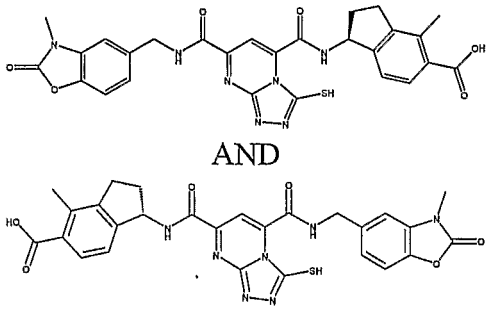
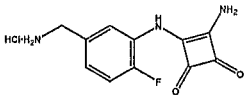
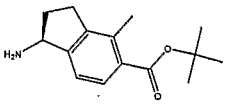
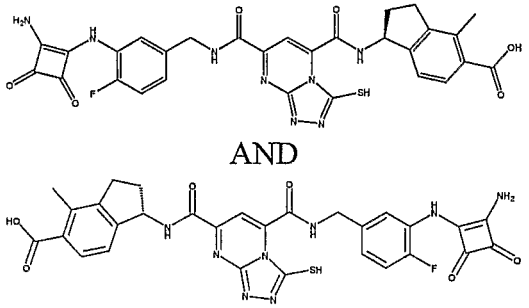
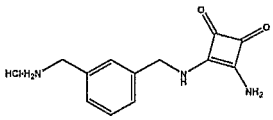
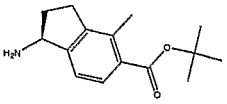
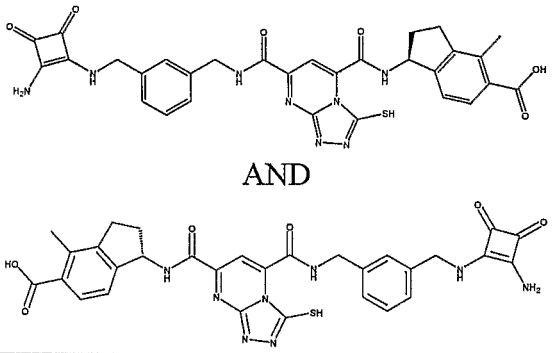
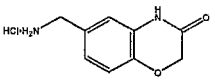
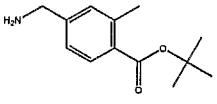
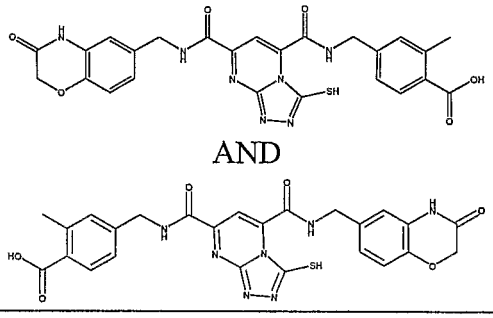
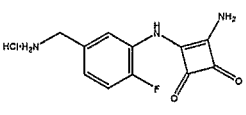
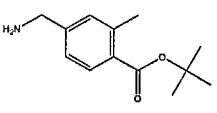
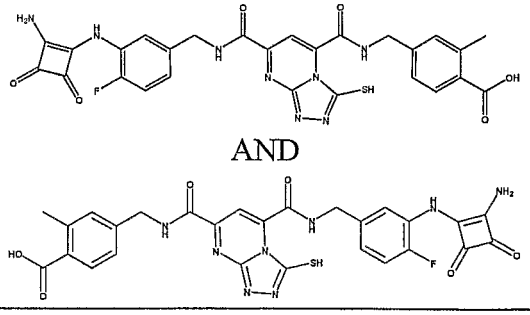
Ex. #	amine (Step B)	amine (Step D)	products
1287			 AND
1288			 AND 
1289			 AND 
1290			 AND 
1291			 AND 

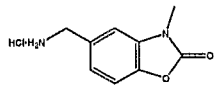
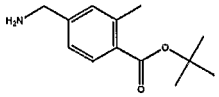
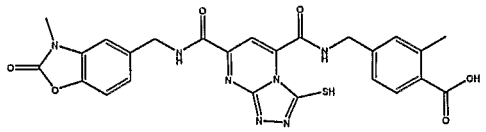
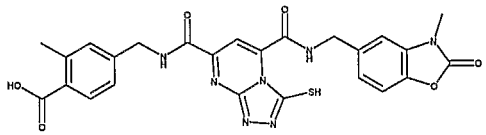
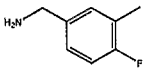
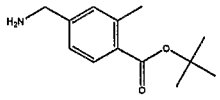
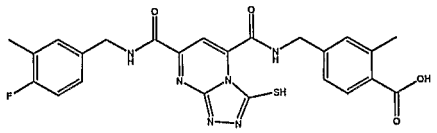
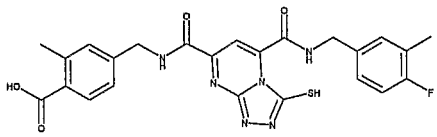
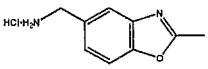
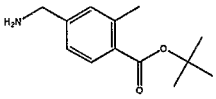
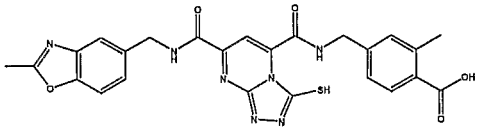
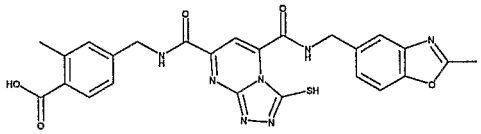
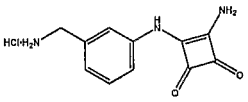
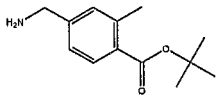
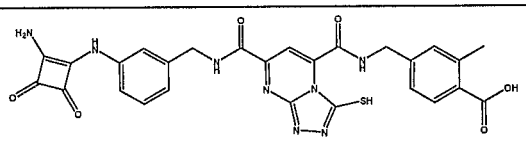
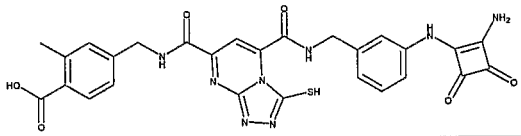
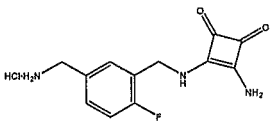
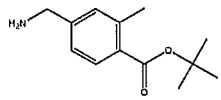
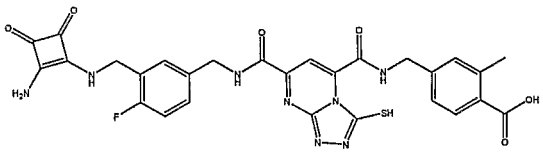
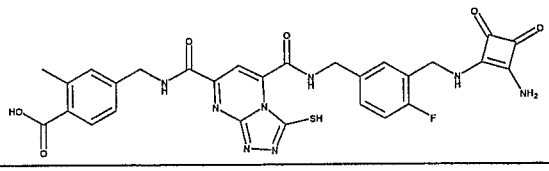
Ex. #	amine (Step B)	amine (Step D)	products
1292			 AND 
1293			 AND 
1294			 AND 

Examples 1295-1304

[0602] If one were to follow a similar procedure as described in the Example 295, Step B to Step E, except using the amines indicated in Table II-23 below in Step B and Step D and thiophosgene instead of phosgene in Step E, and if one were to treat the obtained esters similarly as described in the Example 436, the following compounds would be obtained.

Table II-23

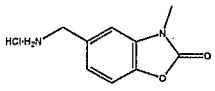
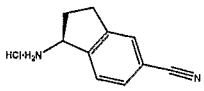
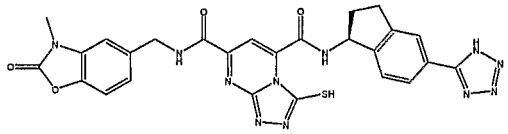
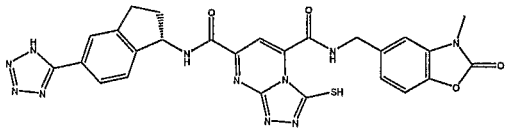
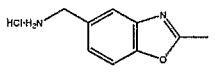
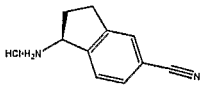
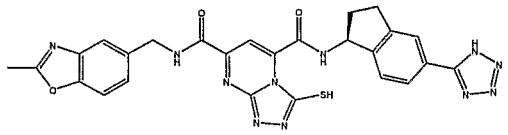
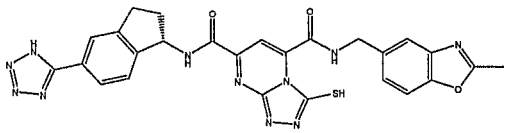
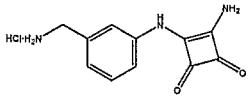
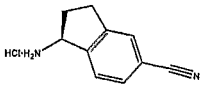
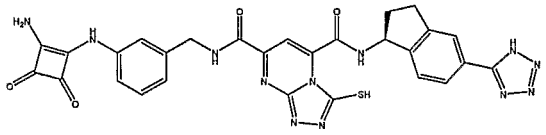
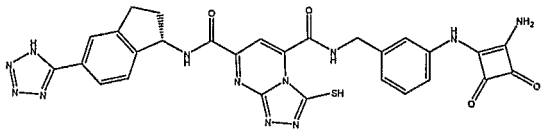
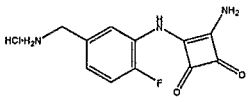
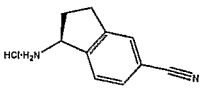
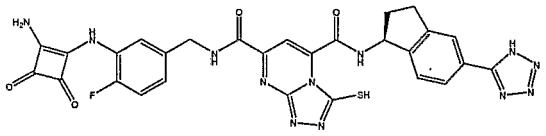
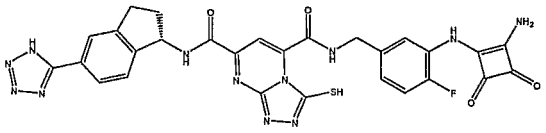
Ex. #	amine (Step B)	amine (Step D)	products
1295			
1296			
1297			
1298			
1299			

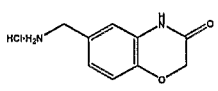
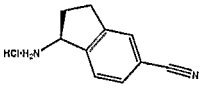
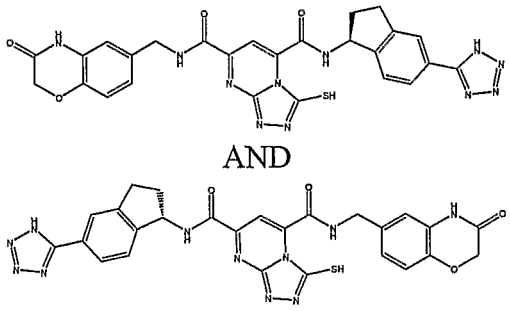
Ex. #	amine (Step B)	amine (Step D)	products
1300			 AND 
1301			 AND 
1302			 AND 
1303			 AND 
1304			 AND 

Examples 1305-1309

[0603] If one were to follow a similar procedure as described in the Example 295, Step B to Step E, except using the amines indicated in Table II-24 below in Step B and Step D and thiophosgene instead of phosgene in Step E, and if one were to treat the obtained nitriles similarly as described in the Example 469, the following compounds would be obtained.

Table II-24

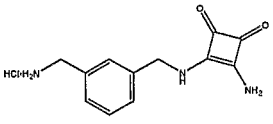
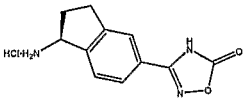
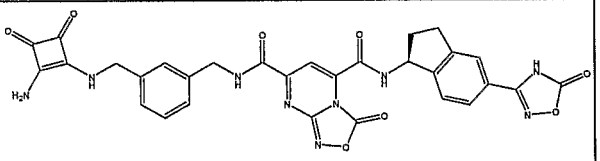
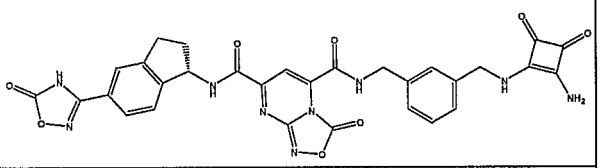
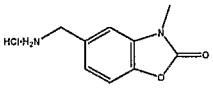
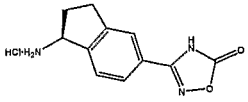
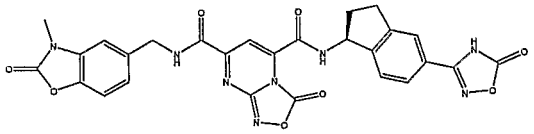
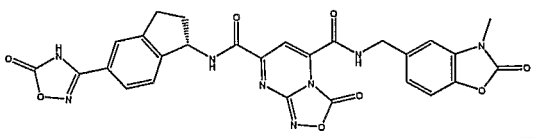
Ex. #	amine (Step B)	amine (Step D)	products
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1306			 AND 
1307			 AND 
1308			 AND 

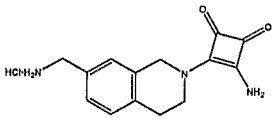
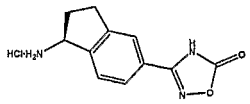
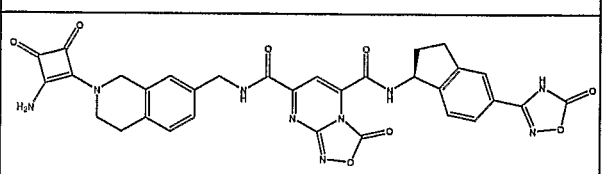
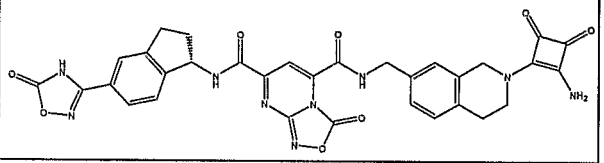
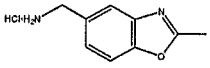
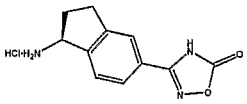
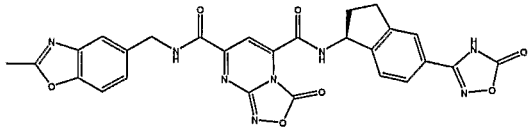
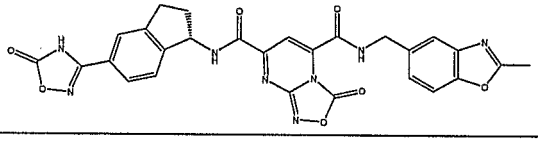
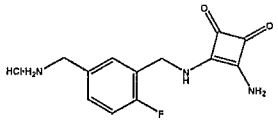
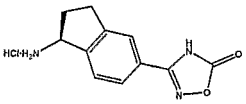
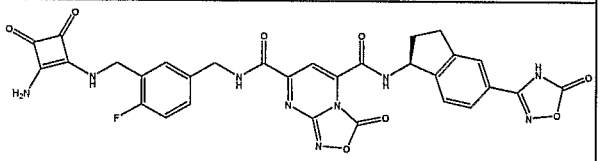
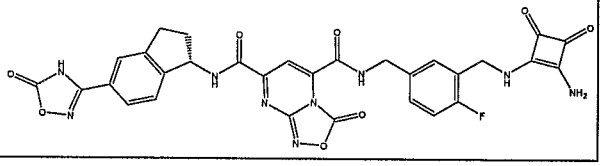
Ex. #	amine (Step B)	amine (Step D)	products
1309			 AND

Examples 1310-1314

[0604] If one were to follow a similar procedure as described in the Example 295, Step B to Step E, except using the amines indicated in Table II-25 below in Step B and Step D and hydroxylamine instead of hydrazine in Step E, the following compounds would be obtained.

Table II-25

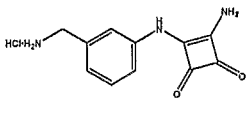
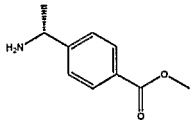
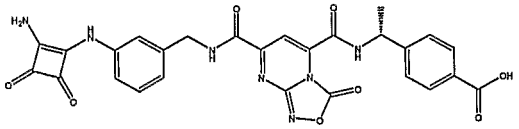
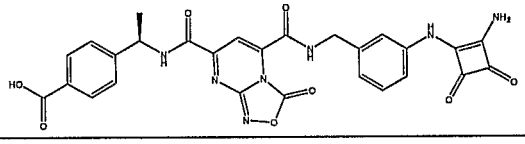
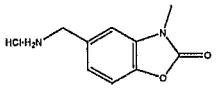
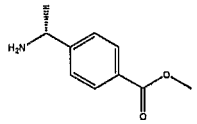
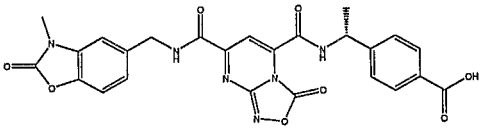
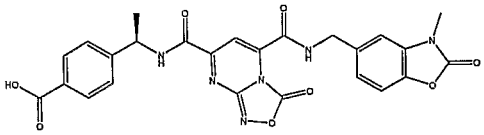
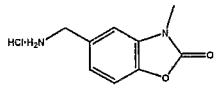
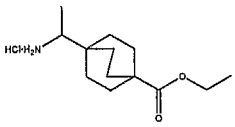
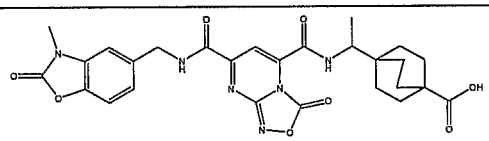
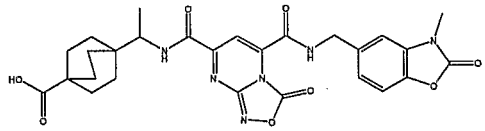
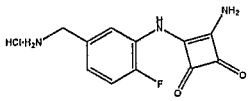
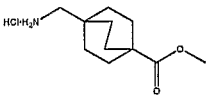
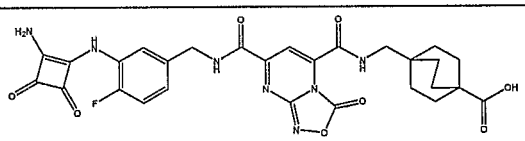
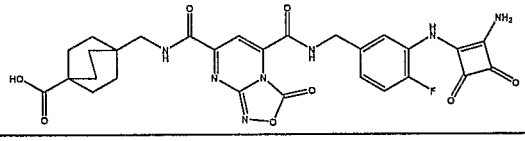
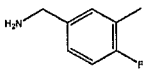
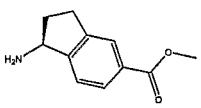
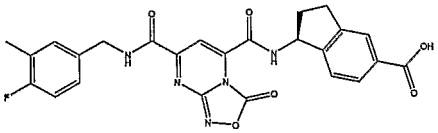
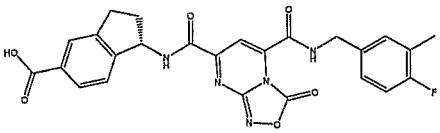
Ex. #	amine (Step B)	amine (Step D)	products
1310			 AND 
1311			 AND 

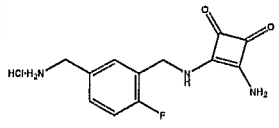
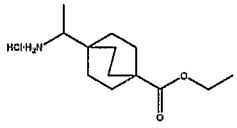
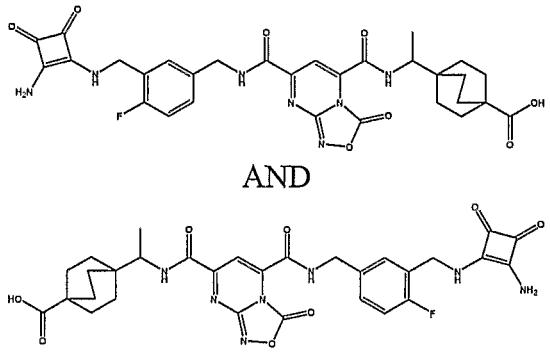
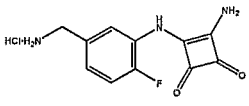
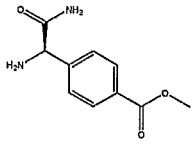
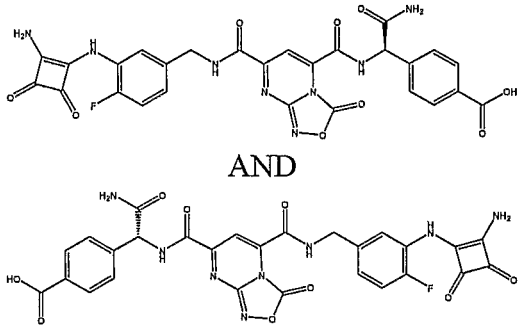
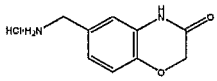
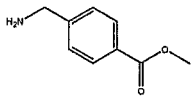
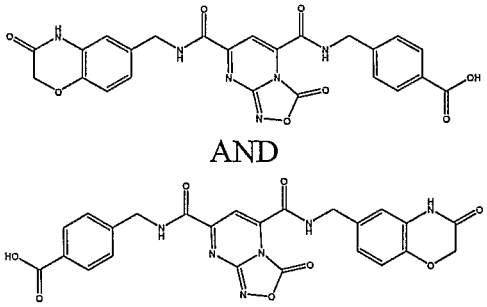
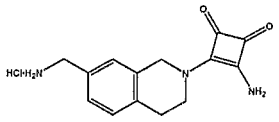
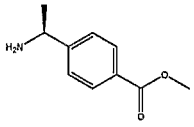
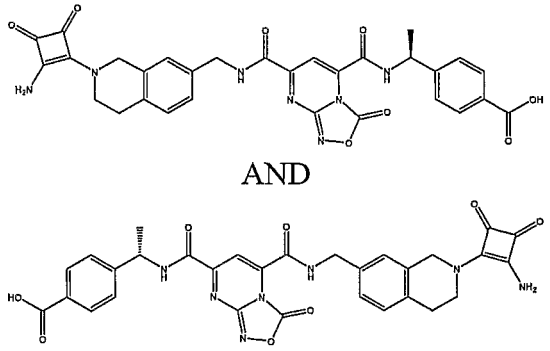
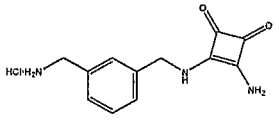
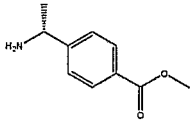
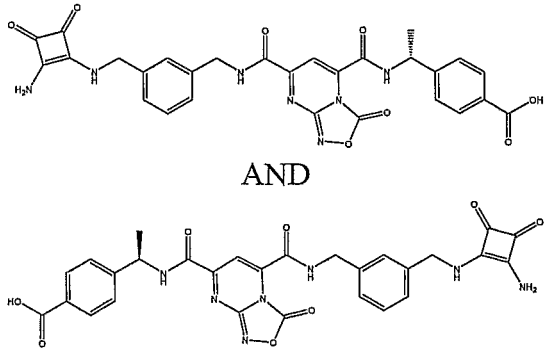
Ex. #	amine (Step B)	amine (Step D)	products
1312			 AND 
1313			 AND 
1314			 AND 

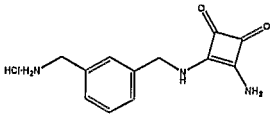
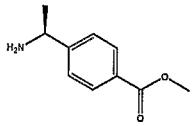
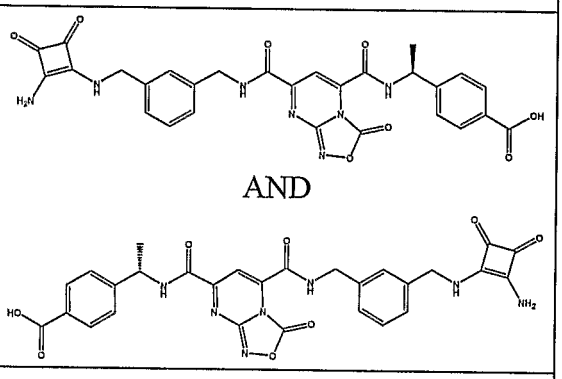
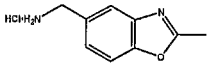
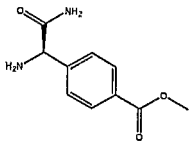
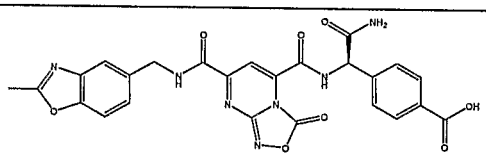
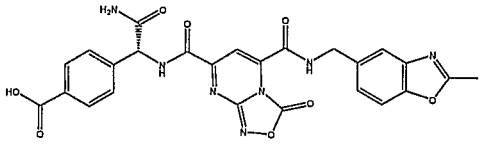
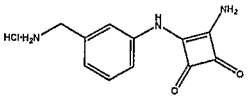
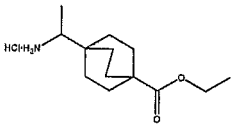
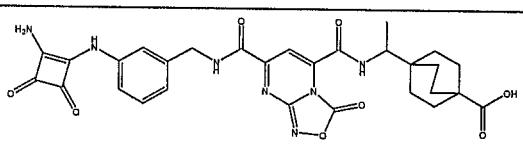
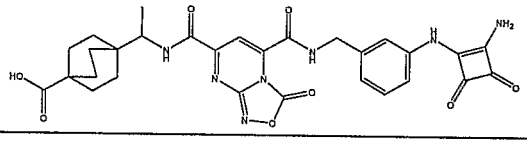
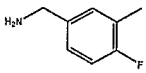
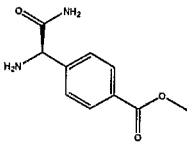
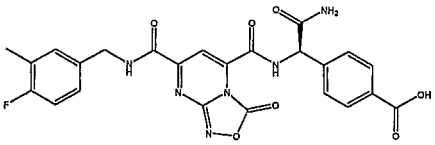
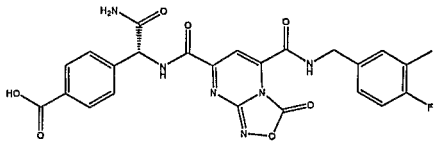
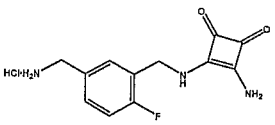
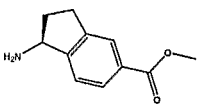
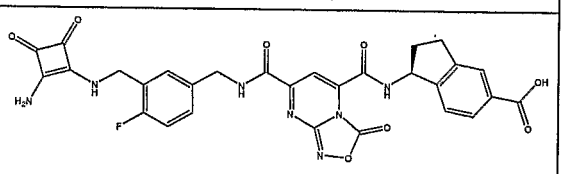
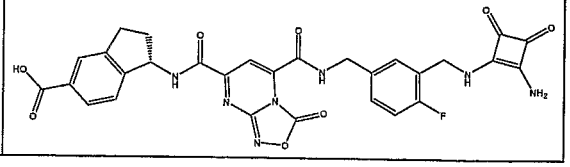
Examples 1315-1334

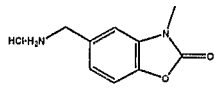
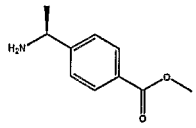
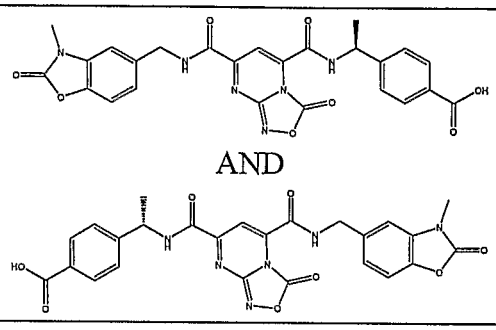
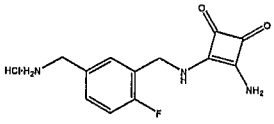
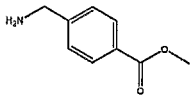
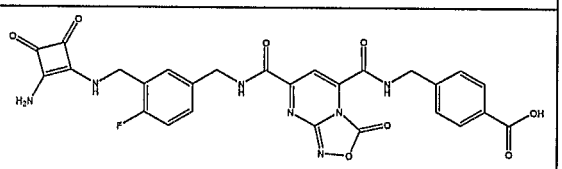
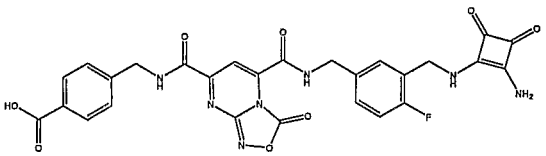
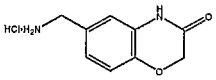
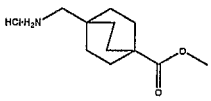
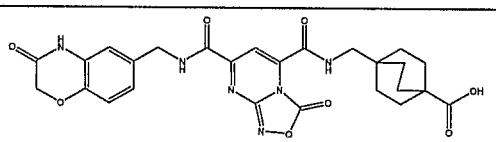
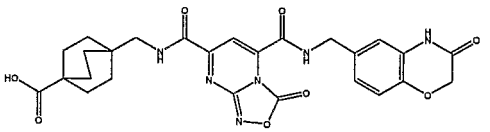
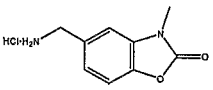
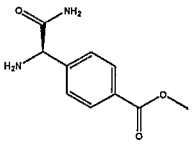
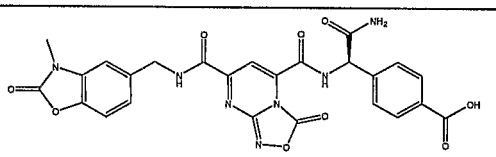
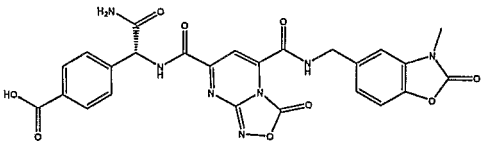
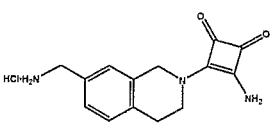
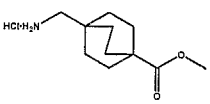
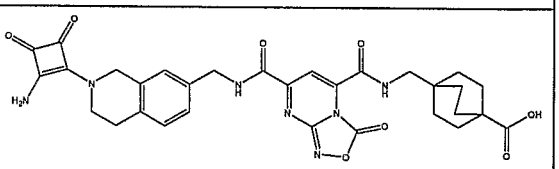
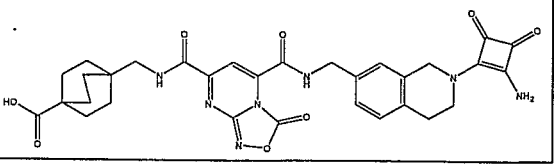
[0605] If one were to follow a similar procedure as described in the Example 295, Step B to Step E, except using the amines indicated in Table II-26 below in Step B and Step D and hydroxylamine instead of hydrazine in Step E, and if one were to treat the obtained esters similarly as described in the Examples 314 or 315, the following compounds would be obtained.

Table II-26

Ex. #	amine (Step B)	amine (Step D)	products
1315			 AND 
1316			 AND 
1317			 AND 
1318			 AND 
1319			 AND 

Ex. #	amine (Step B)	amine (Step D)	products
1320			
1321			
1322			
1323			
1324			

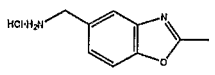
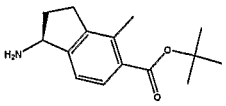
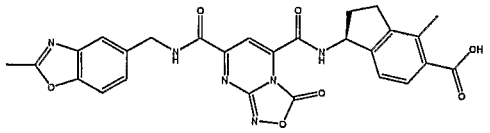
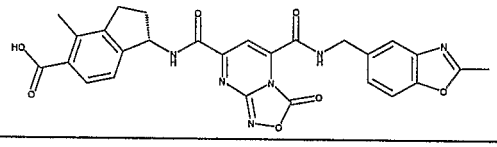
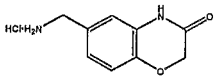
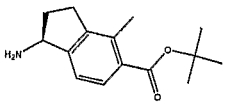
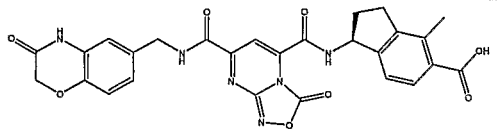
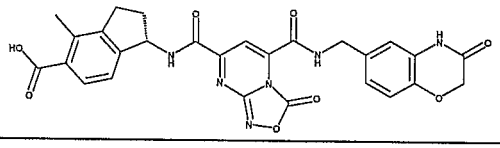
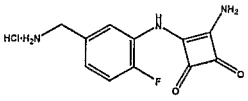
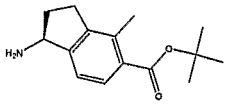
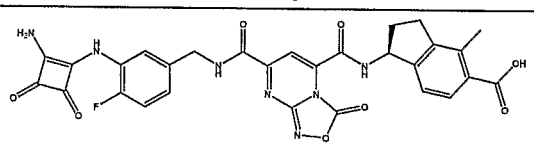
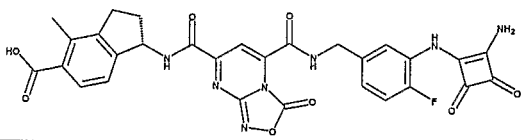
Ex. #	amine (Step B)	amine (Step D)	products
1325			 AND
1326			 AND 
1327			 AND 
1328			 AND 
1329			 AND 

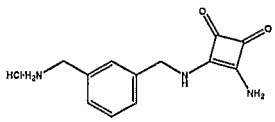
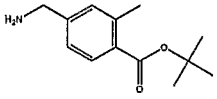
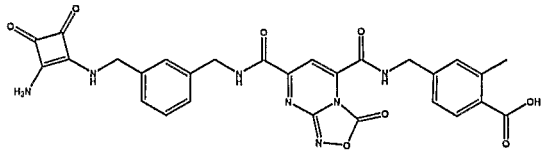
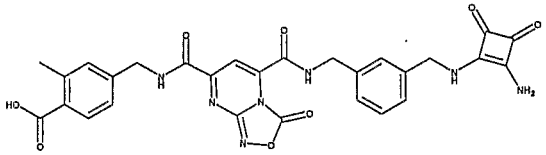
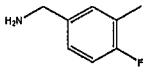
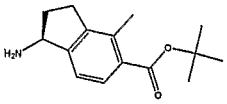
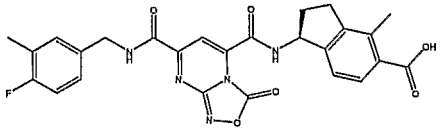
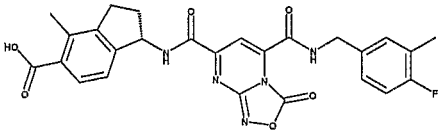
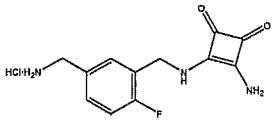
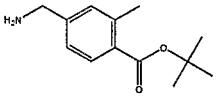
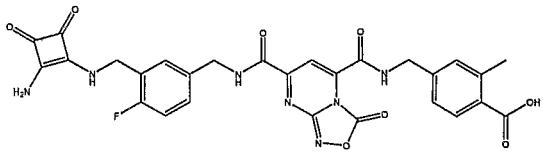
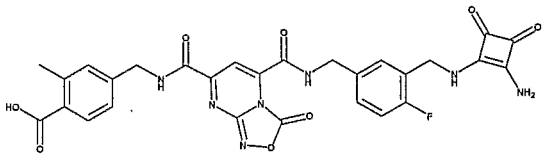
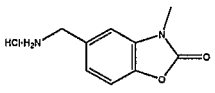
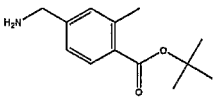
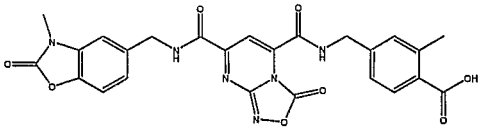
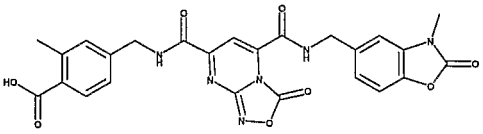
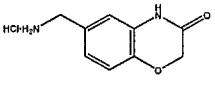
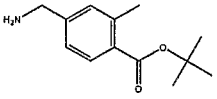
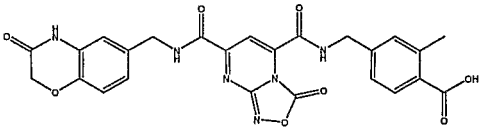
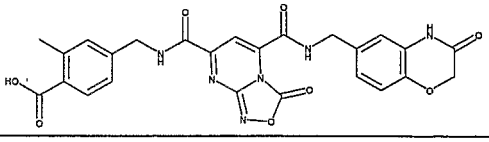
Ex. #	amine (Step B)	amine (Step D)	products
1330			 AND
1331			 AND 
1332			 AND 
1333			 AND 
1334			 AND 

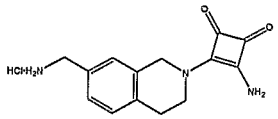
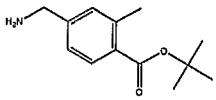
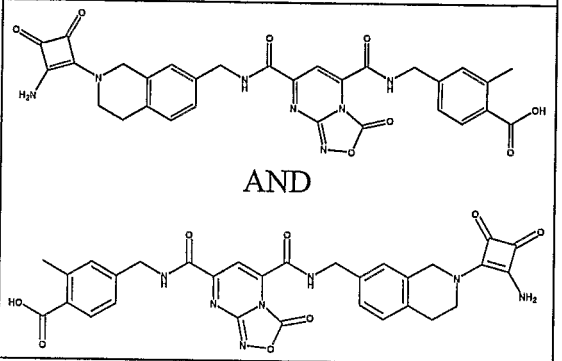
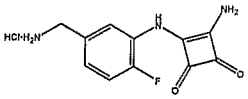
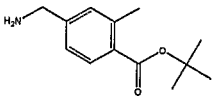
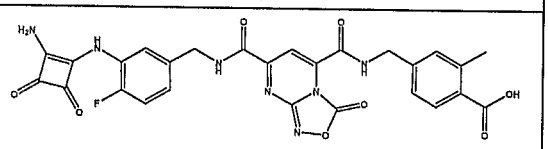
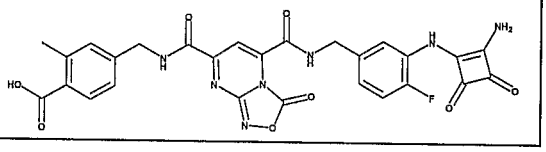
Examples 1335-1344

[0606] If one were to follow a similar procedure as described in the Example 295, Step B to Step E, except using the amines indicated in Table II-27 below in Step B and Step D and hydroxylamine instead of hydrazine in Step E, and if one were to treat the obtained esters similarly as described in the Example 436, the following compounds would be obtained.

Table II-27

Ex. #	amine (Step B)	amine (Step D)	products
1335			 AND 
1336			 AND 
1337			 AND 

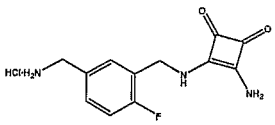
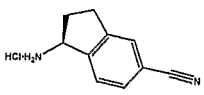
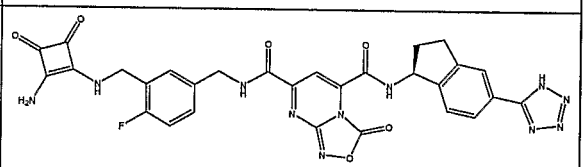
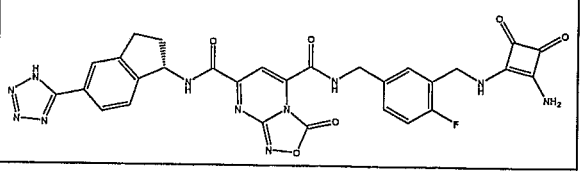
Ex. #	amine (Step B)	amine (Step D)	products
1338			 AND 
1339			 AND 
1340			 AND 
1341			 AND 
1342			 AND 

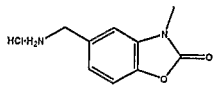
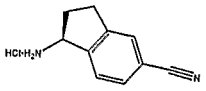
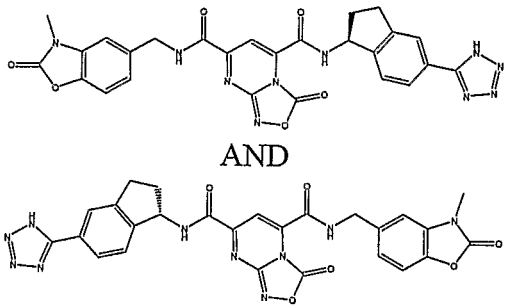
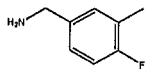
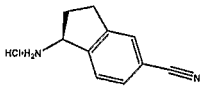
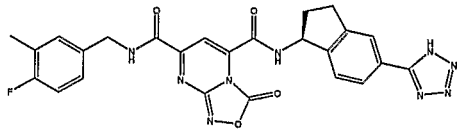
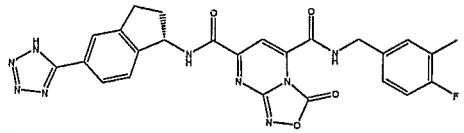
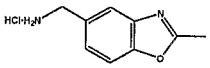
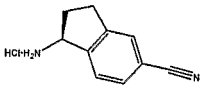
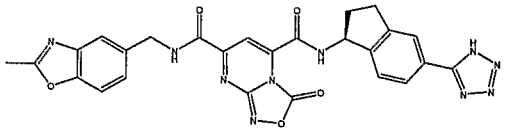
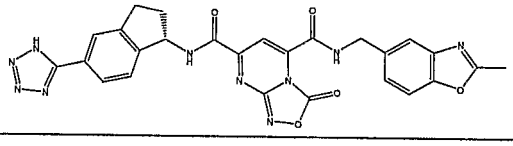
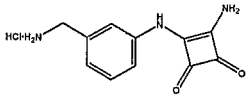
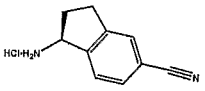
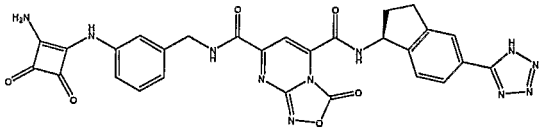
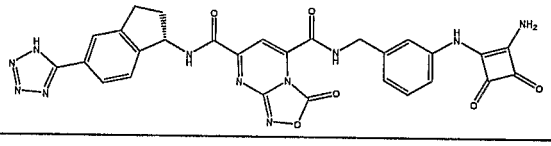
Ex. #	amine (Step B)	amine (Step D)	products
1343			 AND
1344			 AND 

Examples 1345-1349

[0607] If one were to follow a similar procedure as described in the Example 295, Step B to Step E, except using the amines indicated in Table II-28 below in Step B and Step D and hydroxylamine instead of hydrazine in Step E, and if one were to treat the obtained nitriles similarly as described in the Example 469, the following compounds would be obtained.

Table II-28

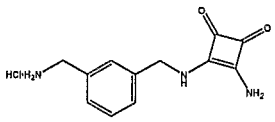
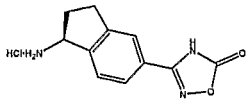
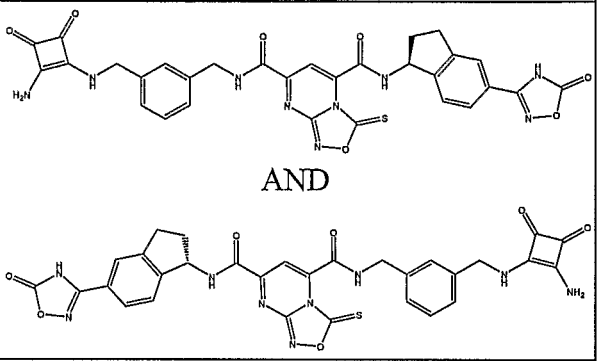
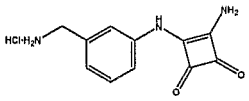
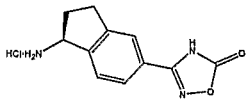
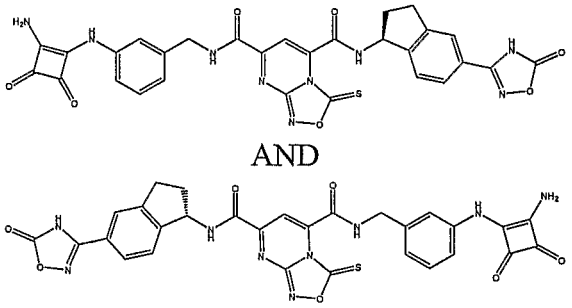
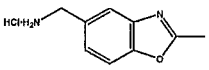
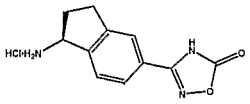
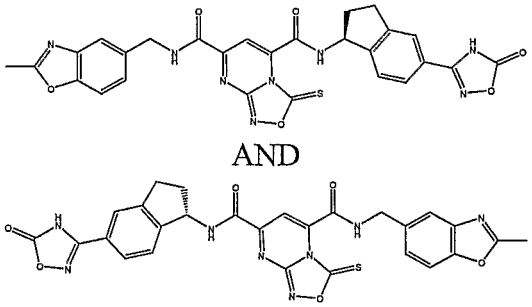
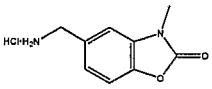
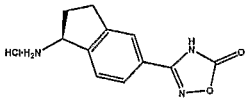
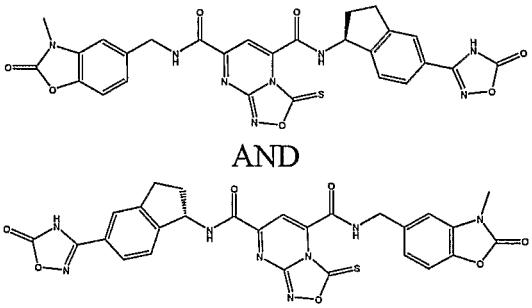
Ex. #	amine (Step B)	amine (Step D)	products
1345			 AND 

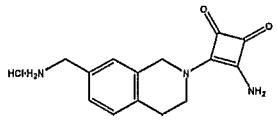
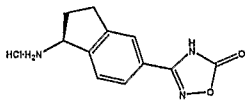
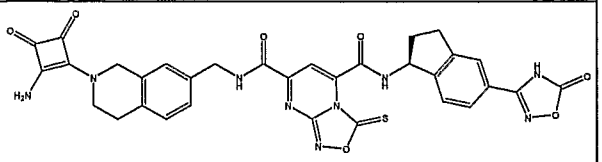
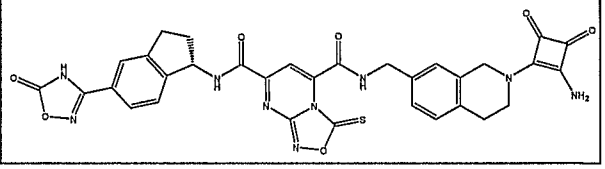
Ex. #	amine (Step B)	amine (Step D)	products
1346			 AND
1347			 AND 
1348			 AND 
1349			 AND 

Examples 1350-1354

[0608] If one were to follow a similar procedure as described in the Example 295, Step B to Step E, except using the amines indicated in Table II-29 below in Step B and Step D and hydroxylamine and thiophosgene instead of hydrazine and phosgene in Step E, the following compounds would be obtained.

Table II-29

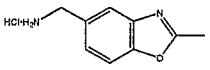
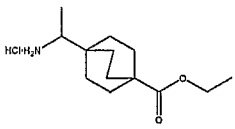
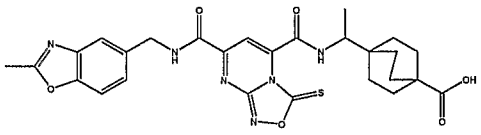
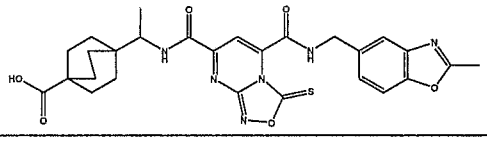
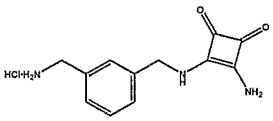
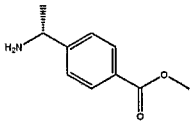
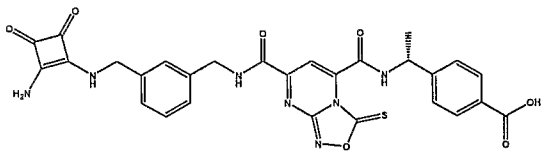
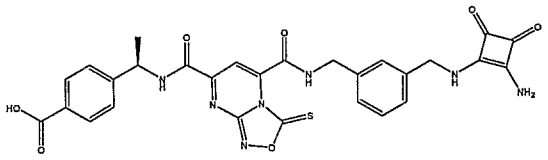
Ex. #	amine (Step B)	amine (Step D)	products
1350			
1351			
1352			
1353			

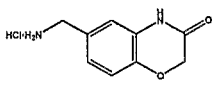
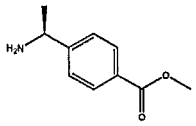
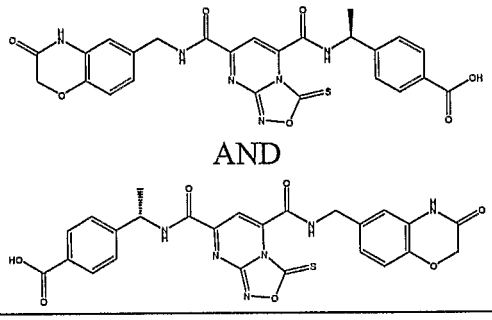
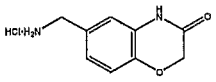
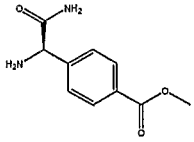
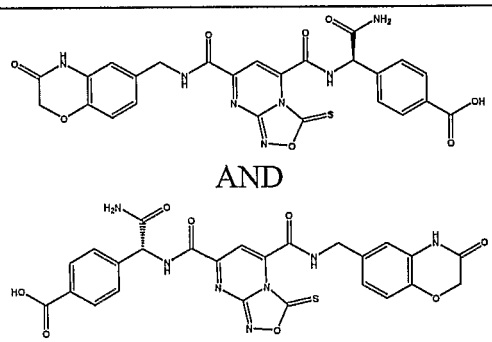
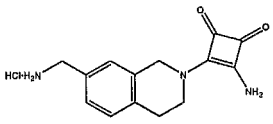
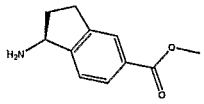
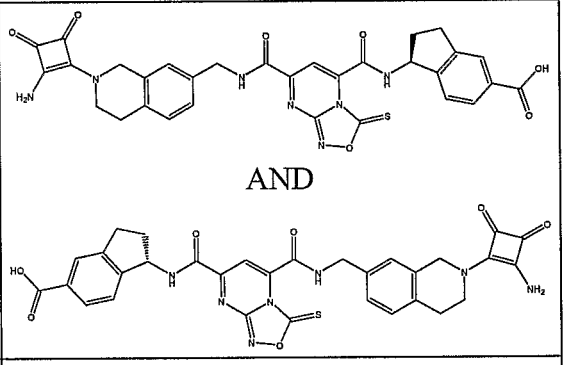
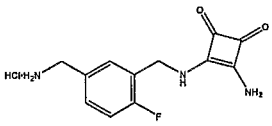
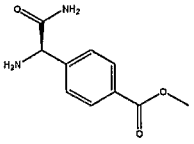
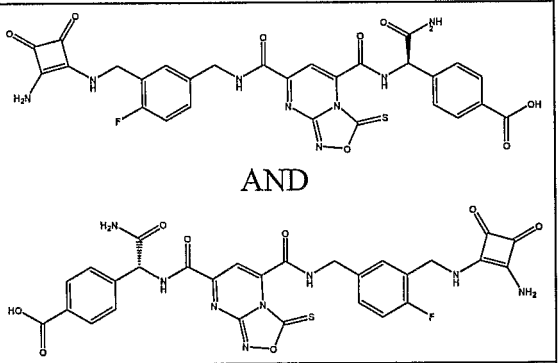
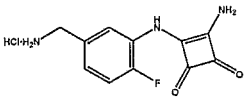
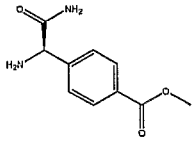
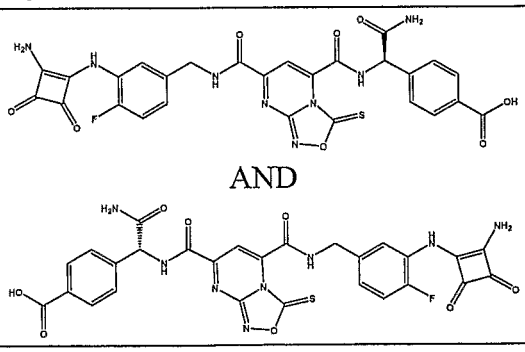
Ex. #	amine (Step B)	amine (Step D)	products
1354			 AND 

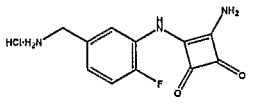
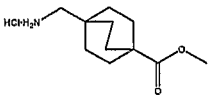
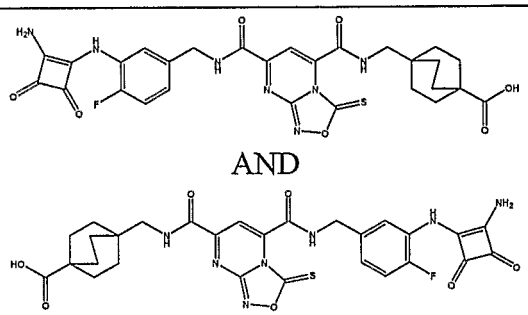
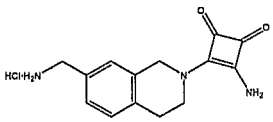
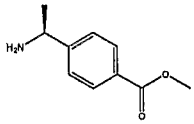
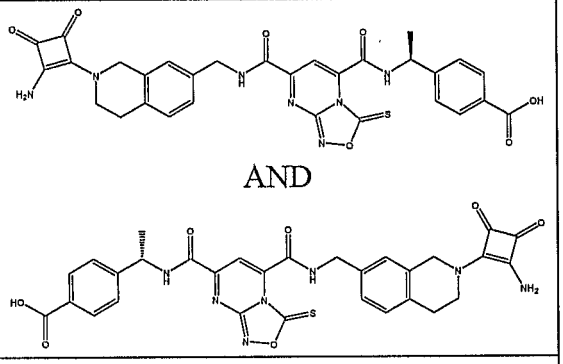
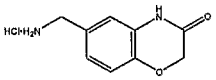
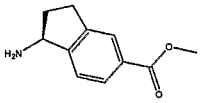
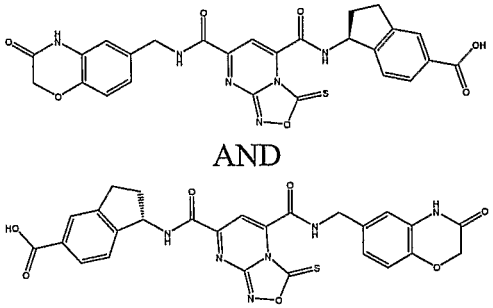
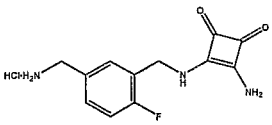
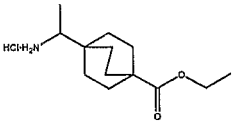
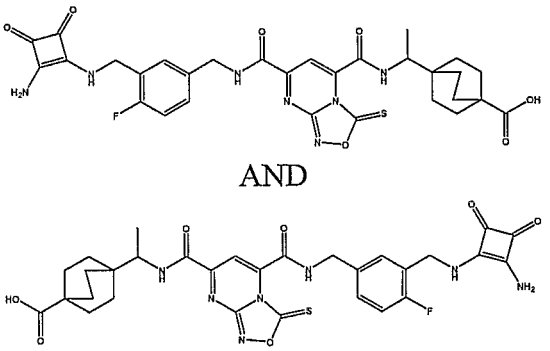
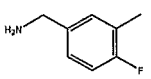
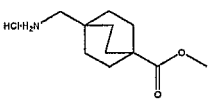
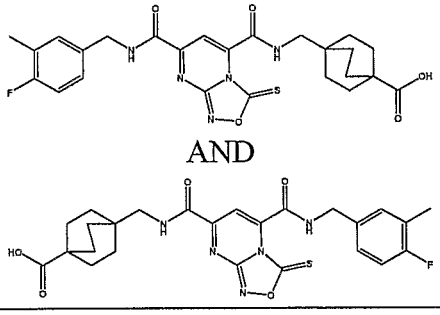
Examples 1355-1374

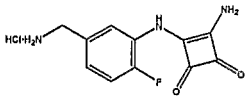
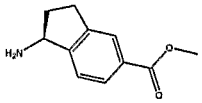
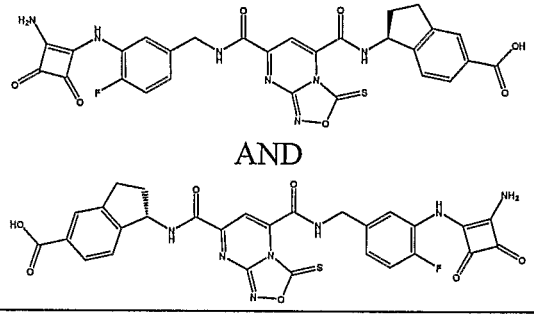
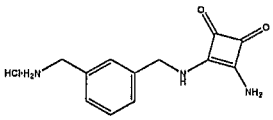
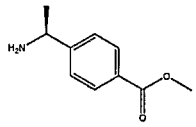
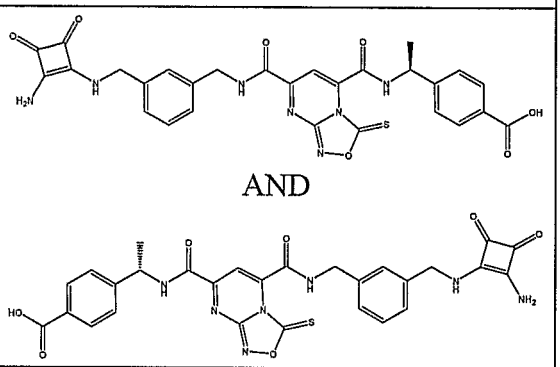
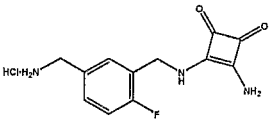
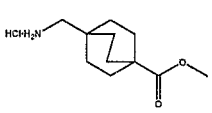
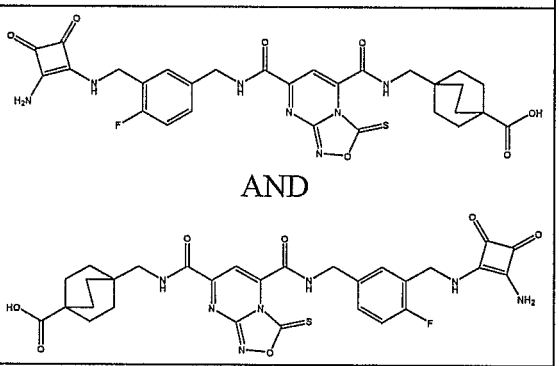
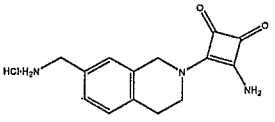
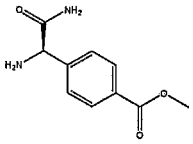
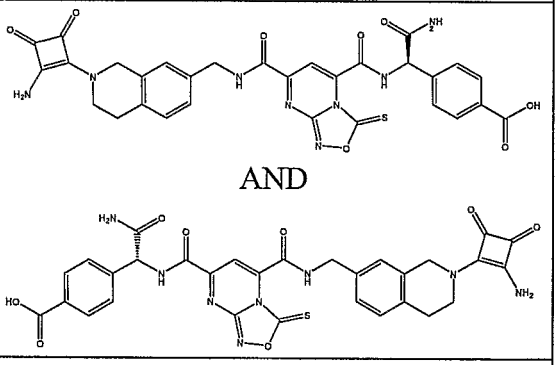
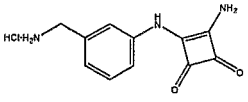
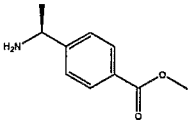
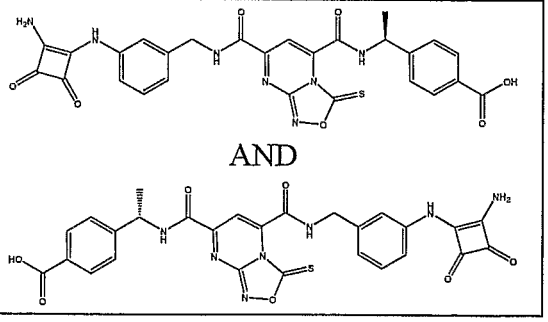
[0609] If one were to follow a similar procedure as described in the Example 295, Step B to Step E, except using the amines indicated in Table II-30 below in Step B and Step D and hydroxylamine and thiophosgene instead of hydrazine and phosgene in Step E, and if one were to treat the obtained esters similarly as described in the Examples 314 or 315, the following compounds would be obtained.

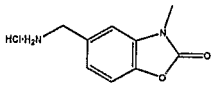
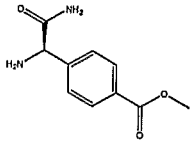
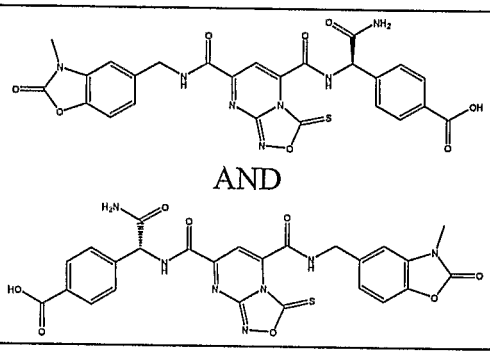
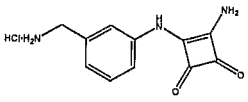
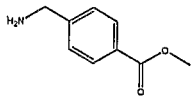
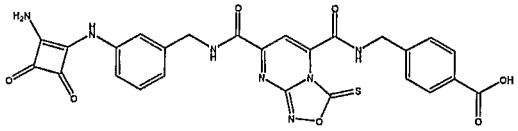
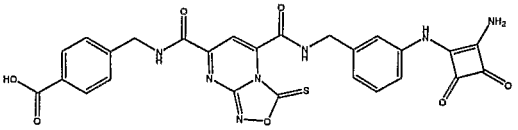
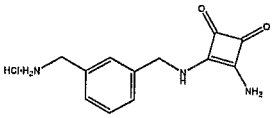
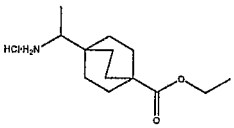
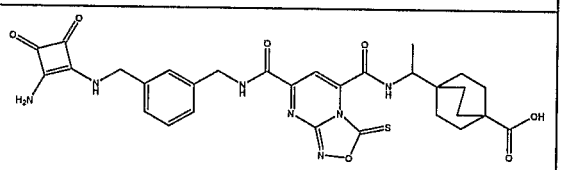
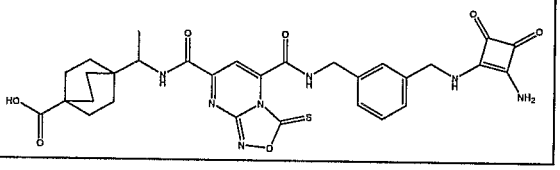
Table II-30

Ex. #	amine (Step B)	amine (Step D)	products
1355			 AND 
1356			 AND 

Ex. #	amine (Step B)	amine (Step D)	products
1357			
1358			
1359			
1360			
1361			

Ex. #	amine (Step B)	amine (Step D)	products
1362			
1363			
1364			
1365			
1366			

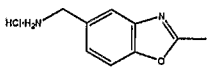
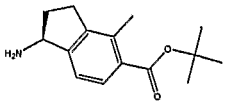
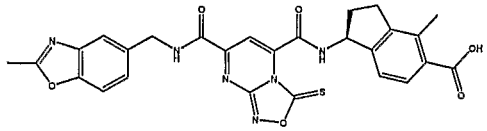
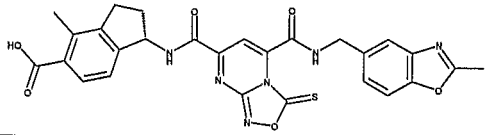
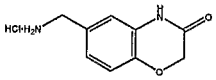
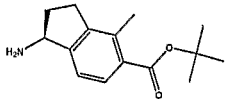
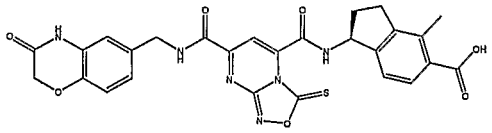
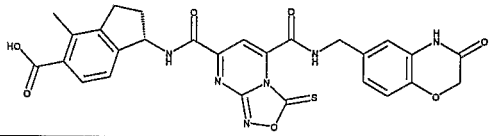
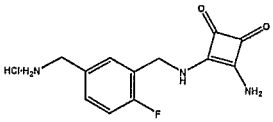
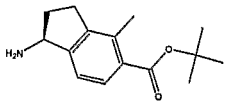
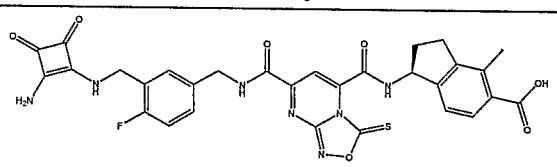
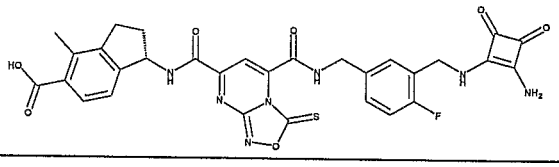
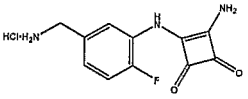
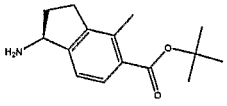
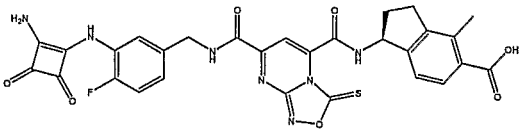
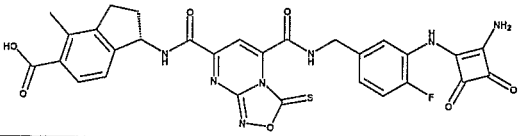
Ex. #	amine (Step B)	amine (Step D)	products
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1368			
1369			
1370			
1371			

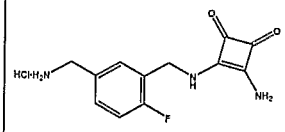
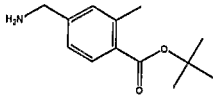
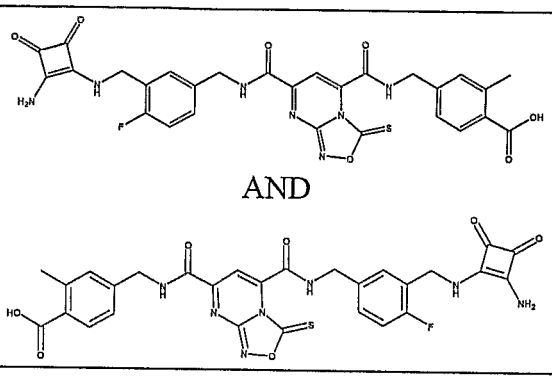
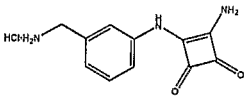
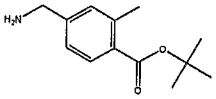
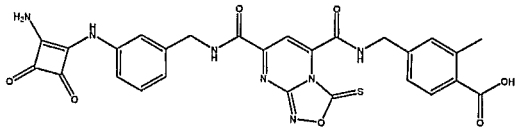
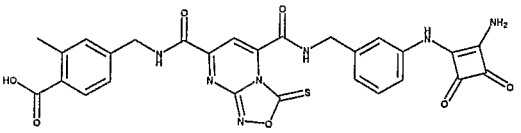
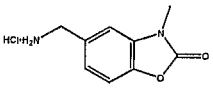
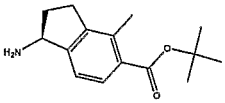
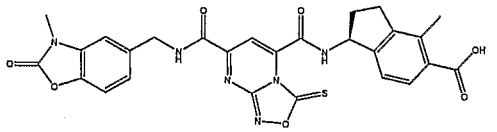
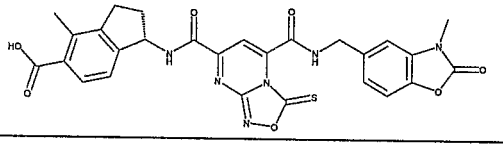
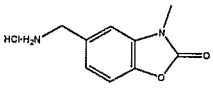
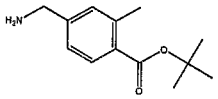
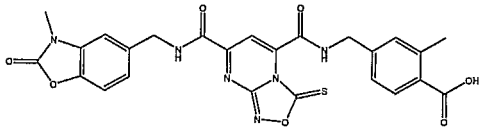
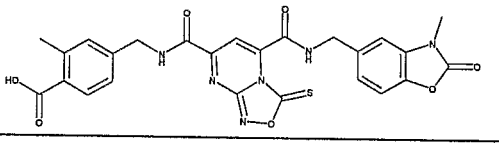
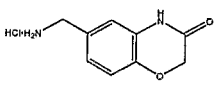
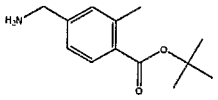
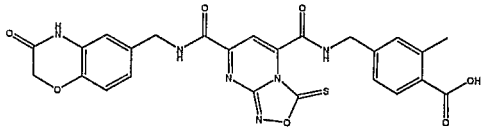
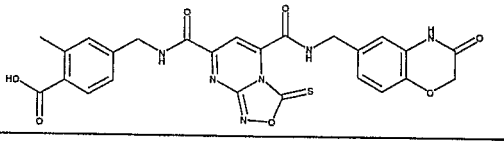
Ex. #	amine (Step B)	amine (Step D)	products
1372			 AND
1373			 AND 
1374			 AND 

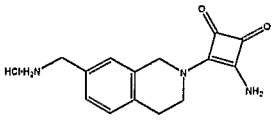
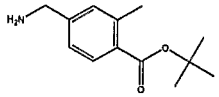
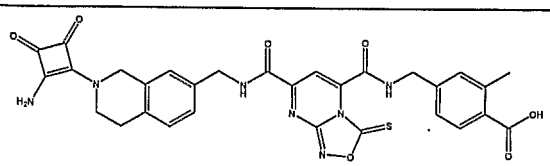
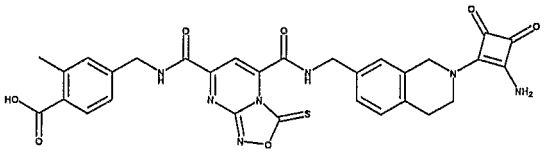
Examples 1375-1384

[0610] If one were to follow a similar procedure as described in the Example 295, Step B to Step E, except using the amines indicated in Table II-31 below in Step B and Step D and hydroxylamine and thiophosgene instead of hydrazine and phosgene in Step E, and if one were to treat the obtained esters similarly as described in the Example 436, the following compounds would be obtained.

Table II-31

Ex. #	amine (Step B)	amine (Step D)	products
1375			 AND 
1376			 AND 
1377			 AND 
1378			 AND 

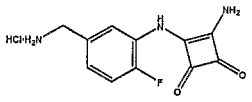
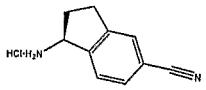
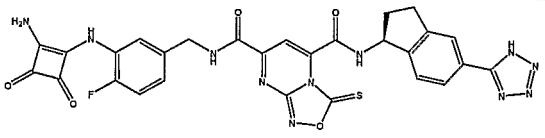
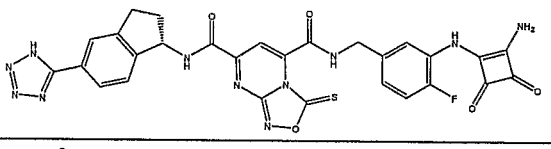
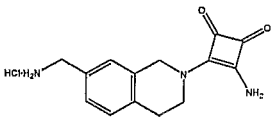
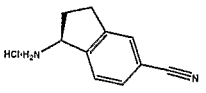
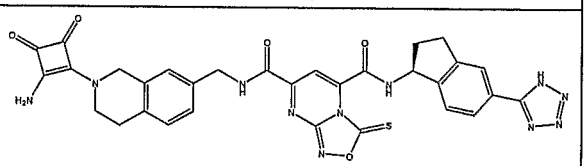
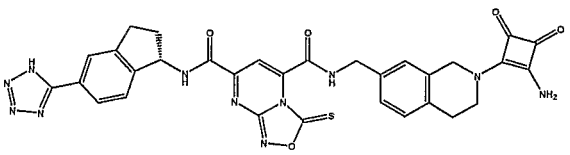
Ex. #	amine (Step B)	amine (Step D)	products
1379			 AND
1380			 AND 
1381			 AND 
1382			 AND 
1383			 AND 

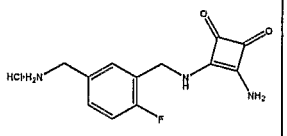
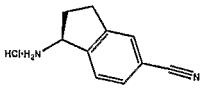
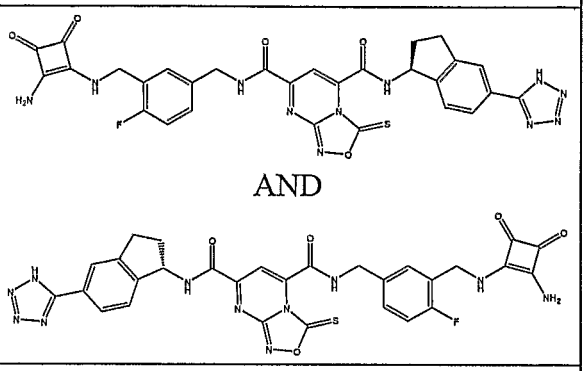
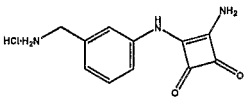
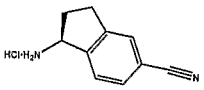
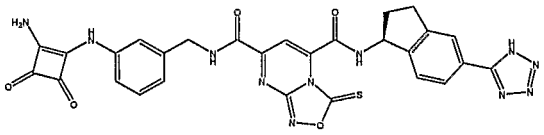
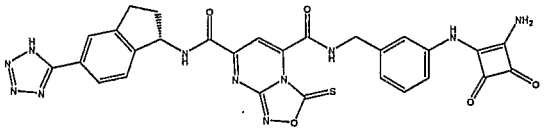
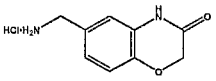
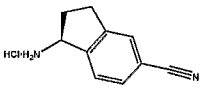
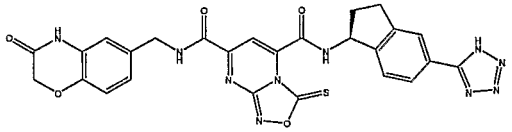
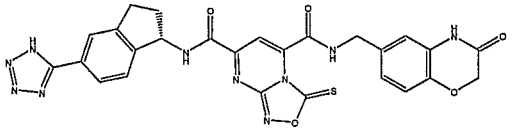
Ex. #	amine (Step B)	amine (Step D)	products
1384			 AND 

Examples 1385-1389

[0611] If one were to follow a similar procedure as described in the Example 295, Step B to Step E, except using the amines indicated in Table II-32 below in Step B and Step D and hydroxylamine and thiophosgene instead of hydrazine and phosgene in Step E, and if one were to treat the obtained nitriles similarly as described in the Example 469, the following compounds would be obtained.

Table II-32

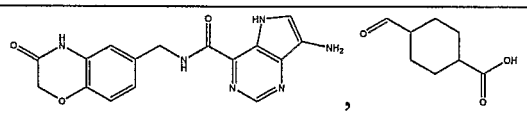
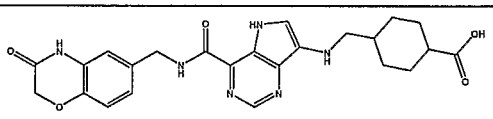
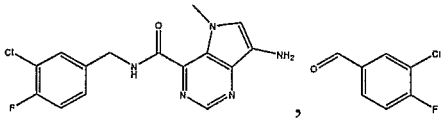
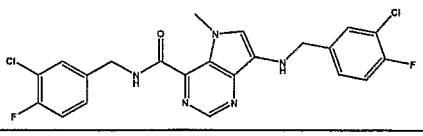
Ex. #	amine (Step B)	amine (Step D)	products
1385			 AND 
1386			 AND 

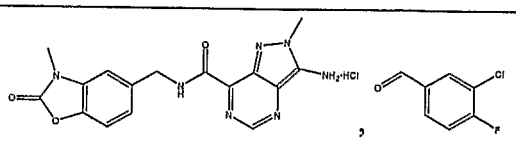
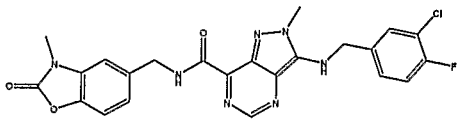
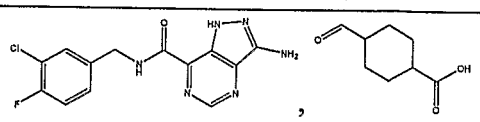
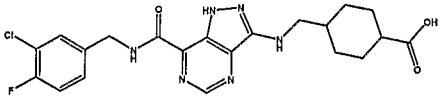
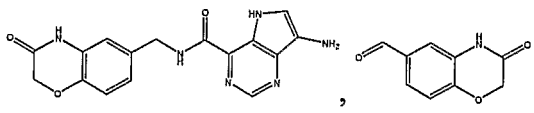
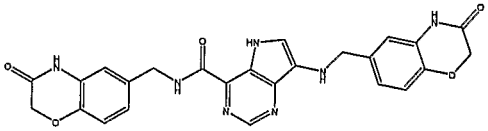
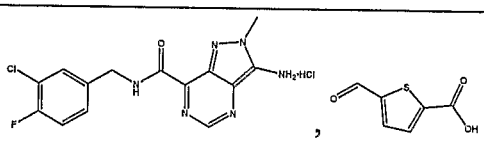
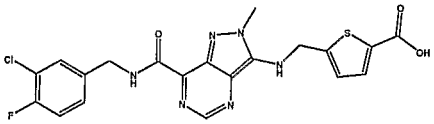
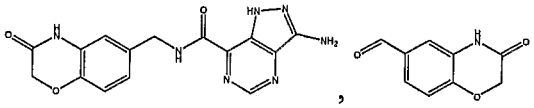
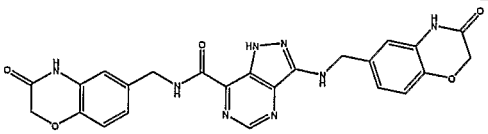
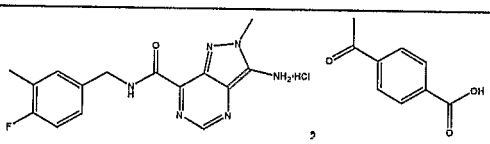
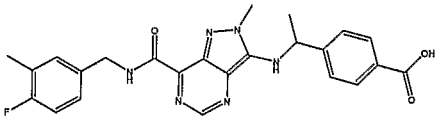
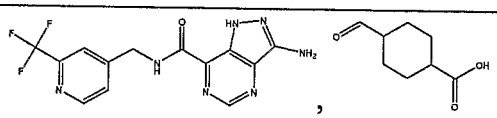
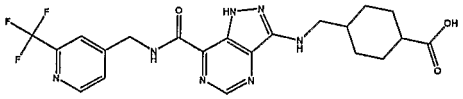
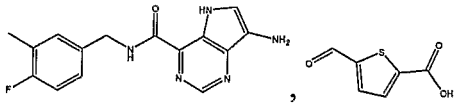
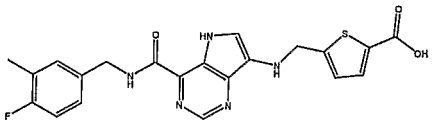
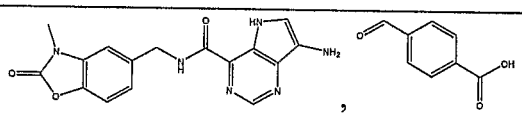
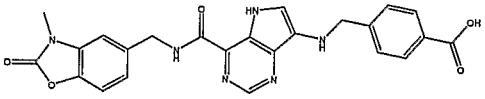
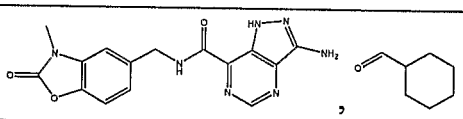
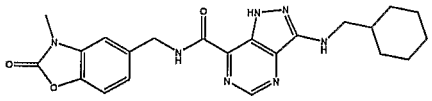
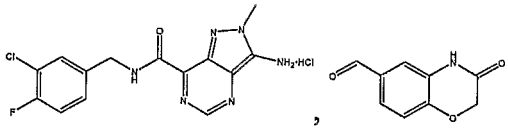
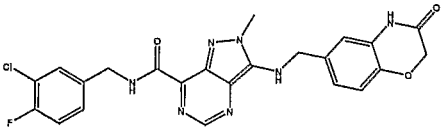
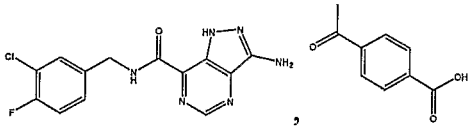
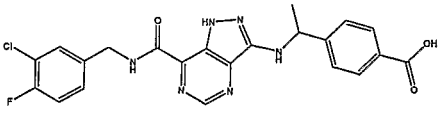
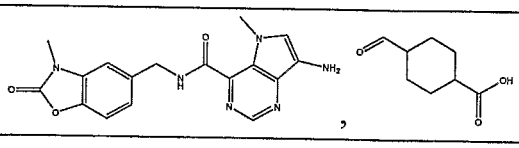
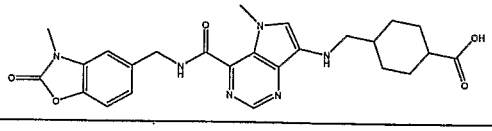
Ex. #	amine (Step B)	amine (Step D)	products
1387			 AND
1388			 AND 
1389			 AND 

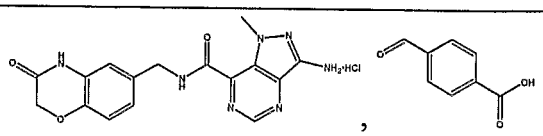
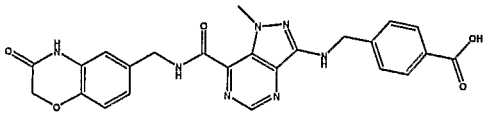
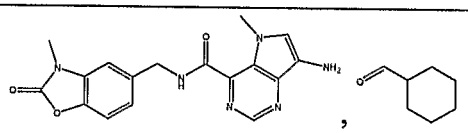
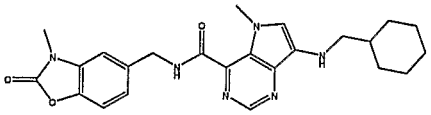
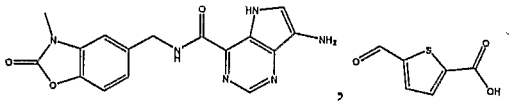
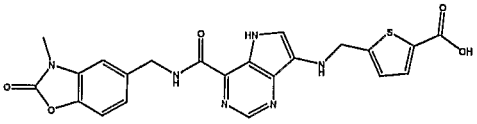
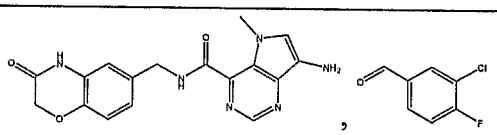
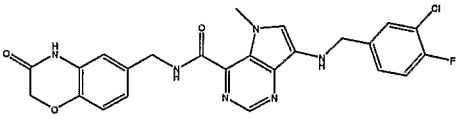
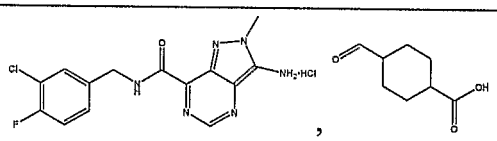
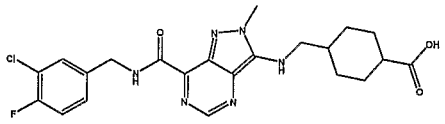
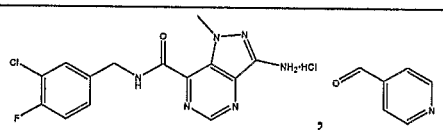
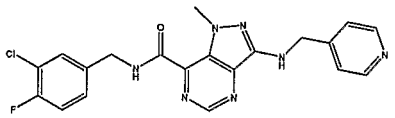
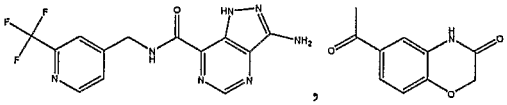
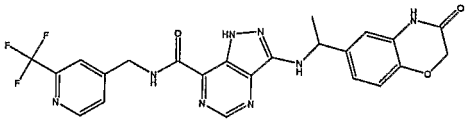
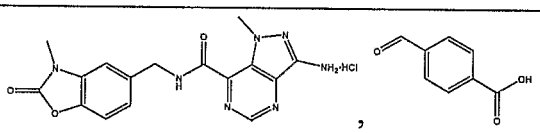
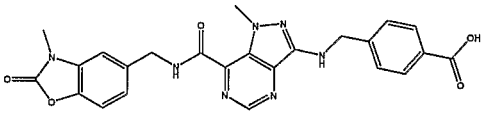
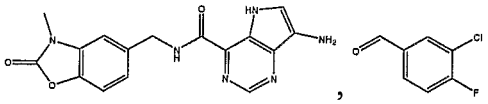
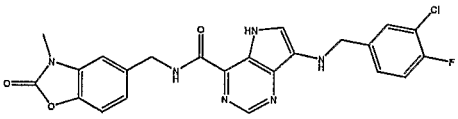
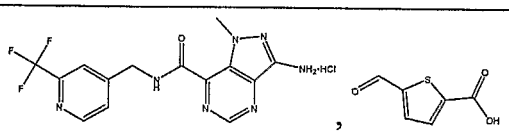
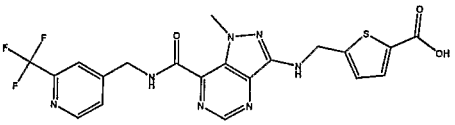
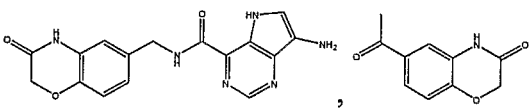
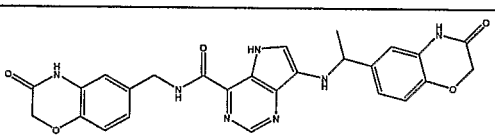
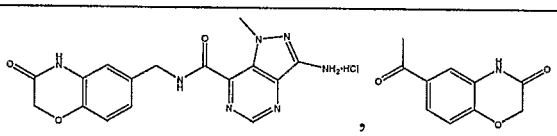
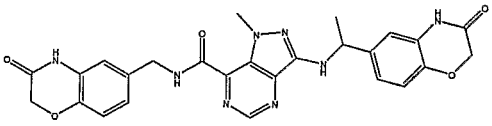
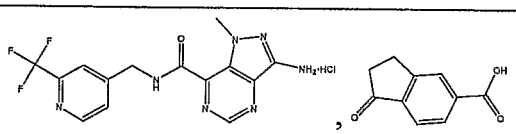
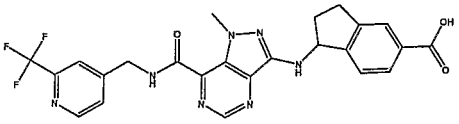
Examples 1390-1489

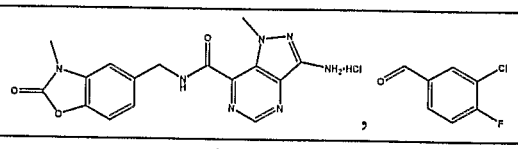
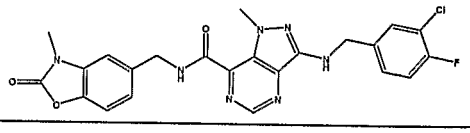
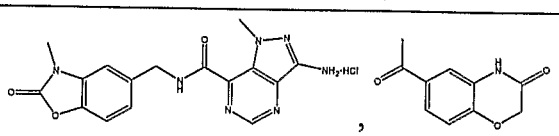
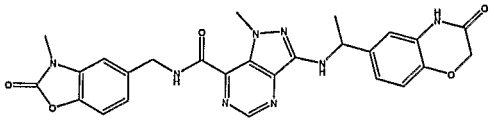
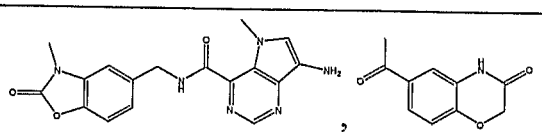
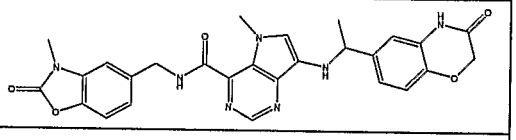
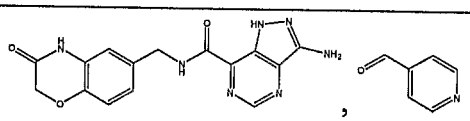
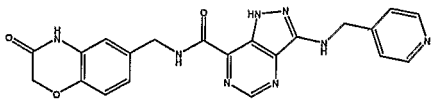
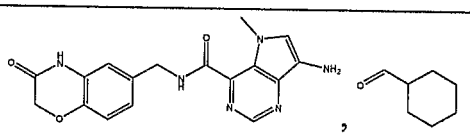
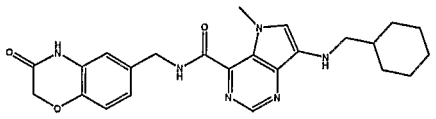
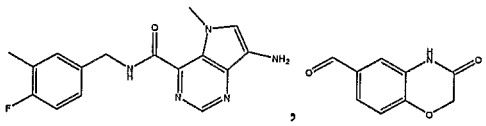
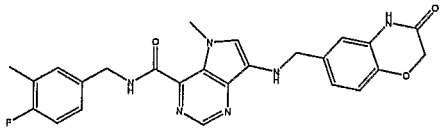
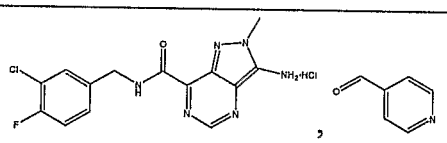
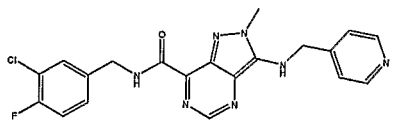
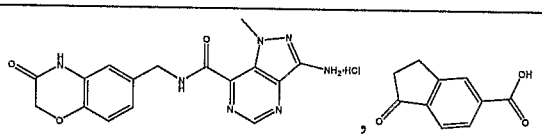
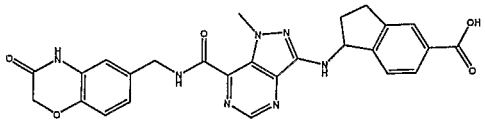
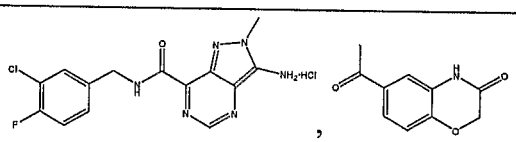
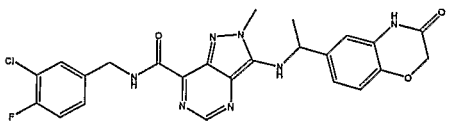
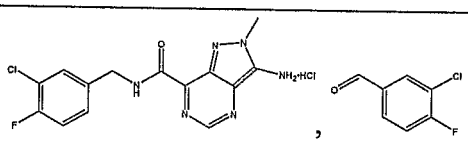
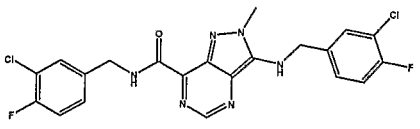
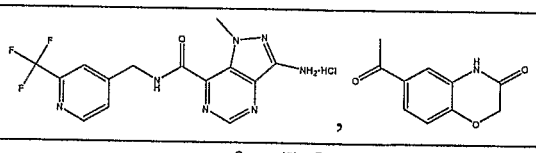
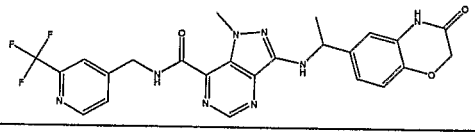
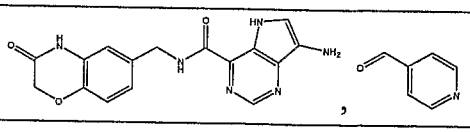
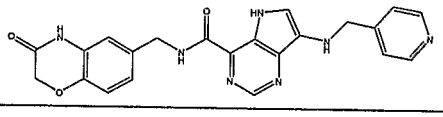
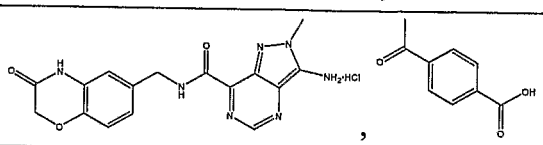
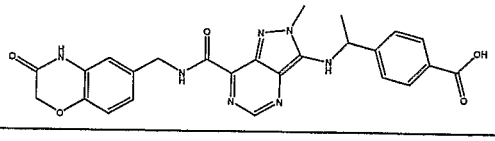
[0612] If one were to follow a similar procedure as described in Example 479, except using the carbonyl compound indicated in Table II-33 below, the following compounds would be obtained.

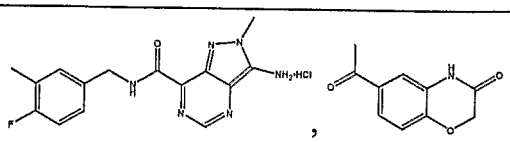
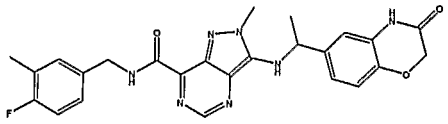
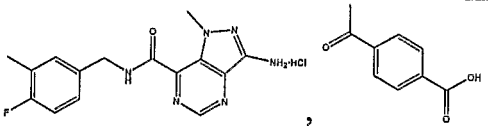
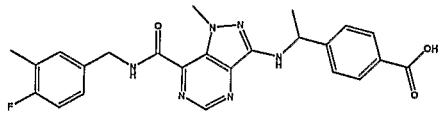
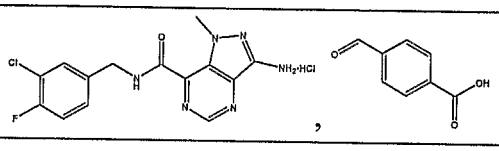
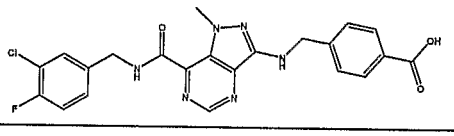
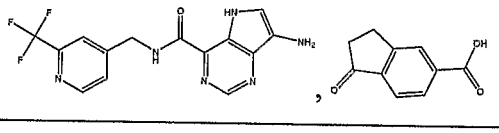
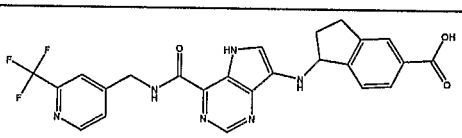
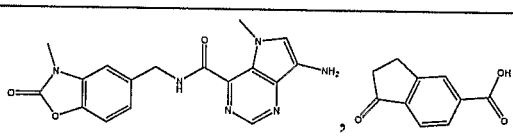
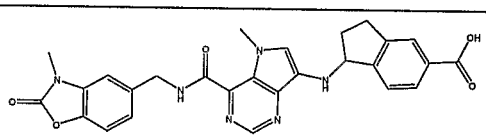
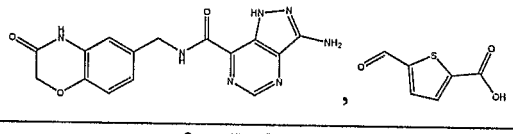
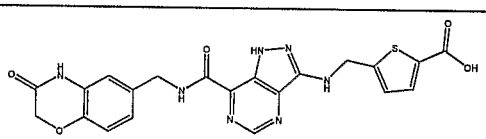
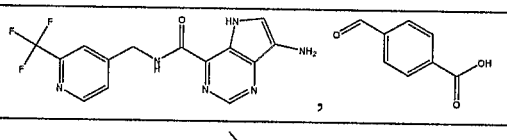
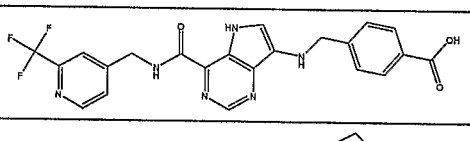
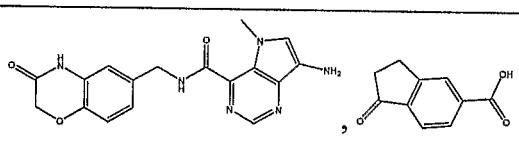
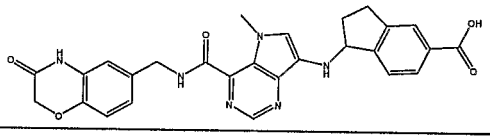
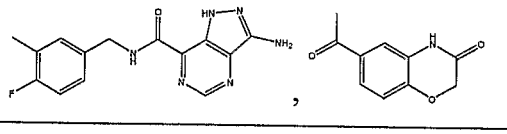
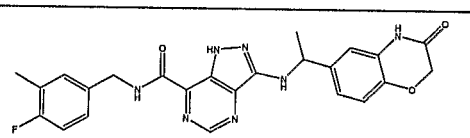
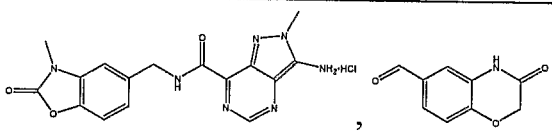
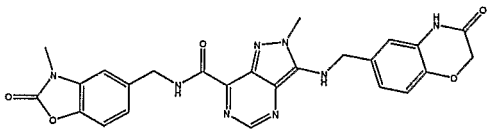
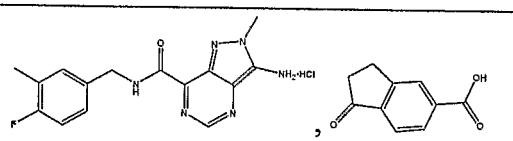
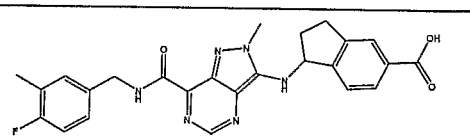
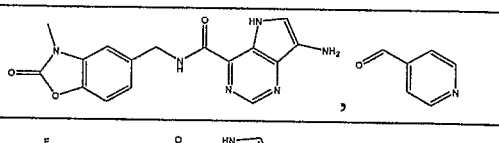
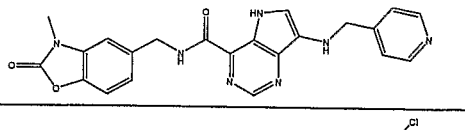
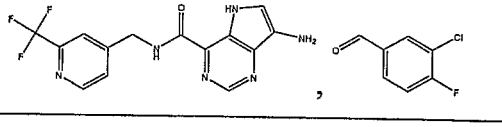
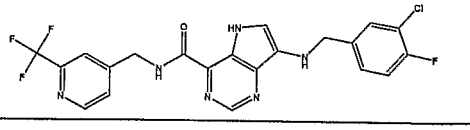
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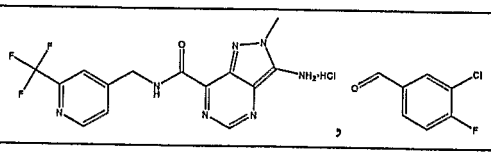
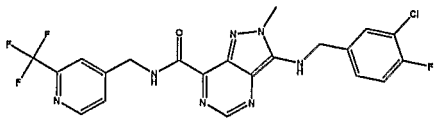
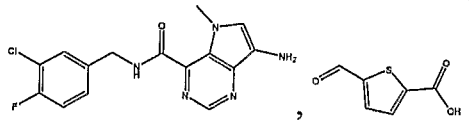
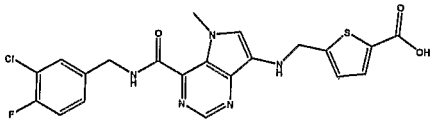
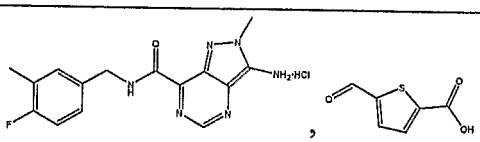
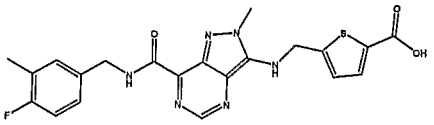
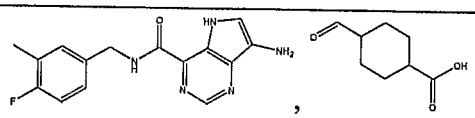
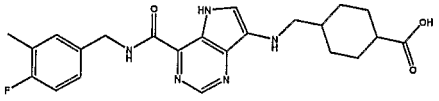
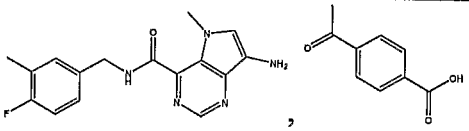
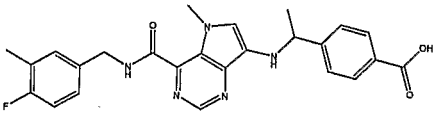
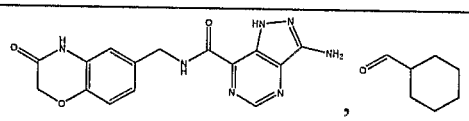
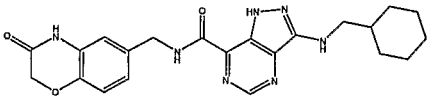
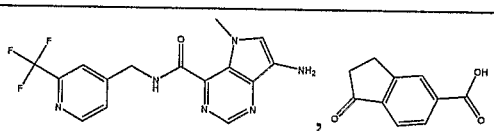
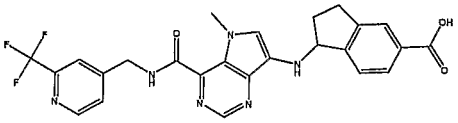
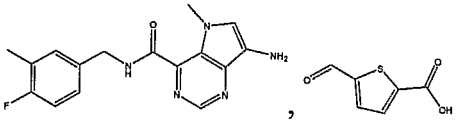
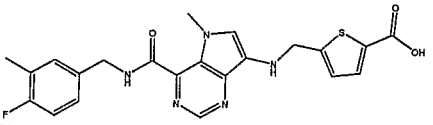
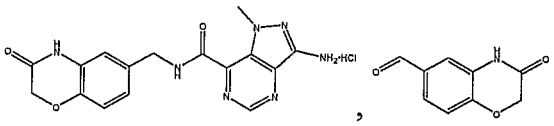
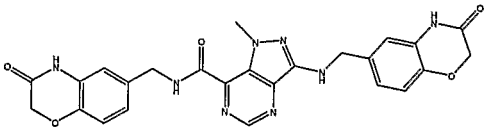
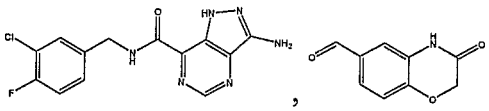
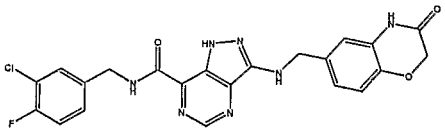
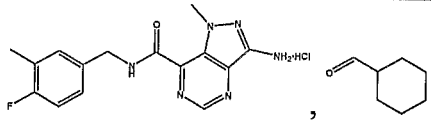
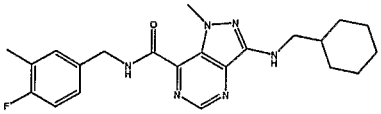
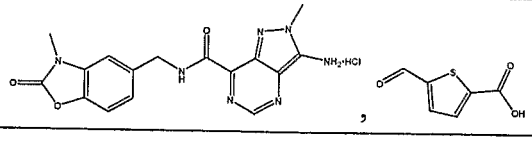
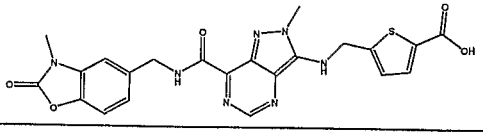
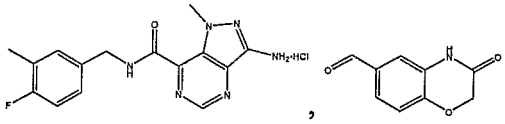
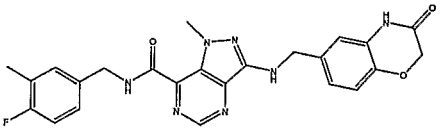
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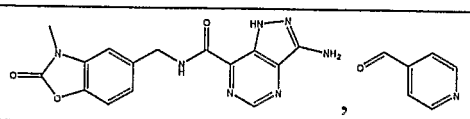
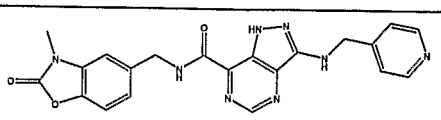
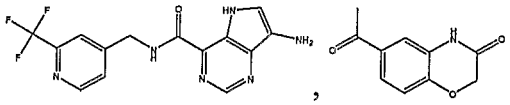
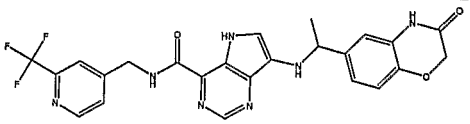
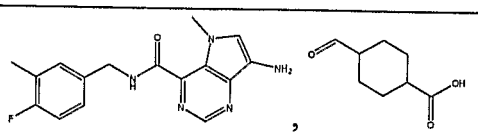
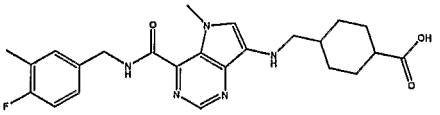
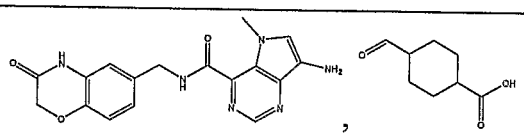
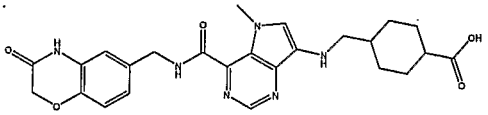
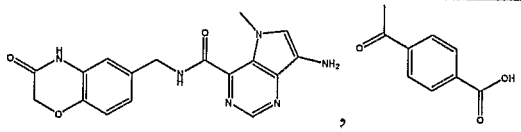
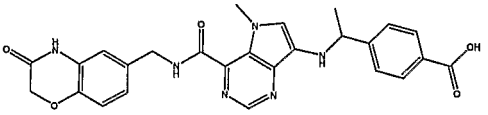
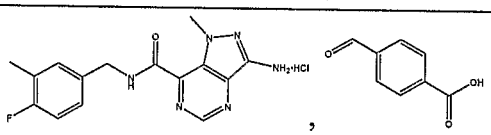
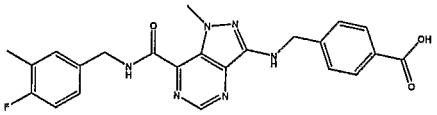
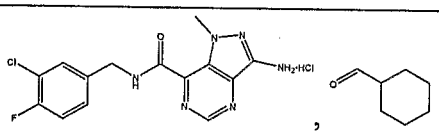
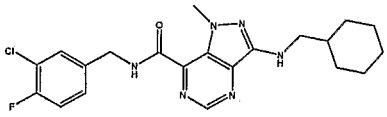
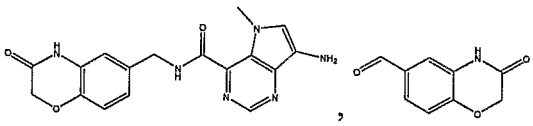
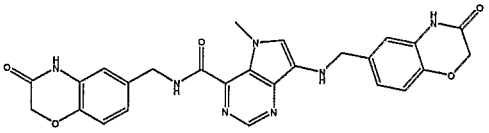
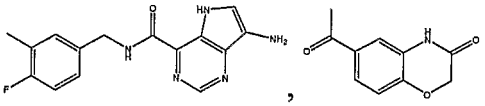
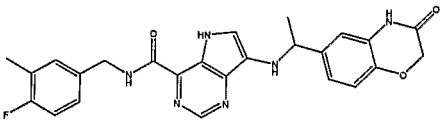
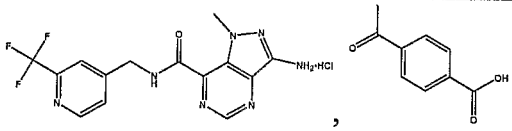
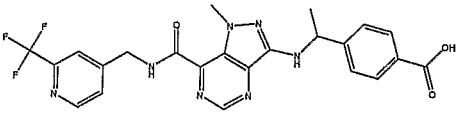
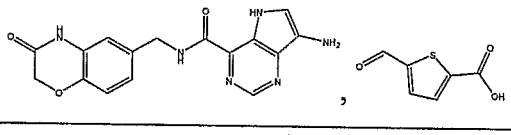
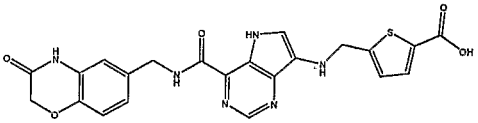
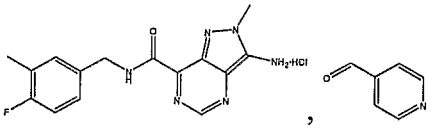
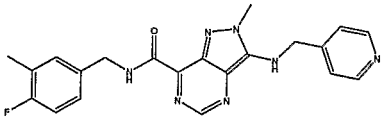
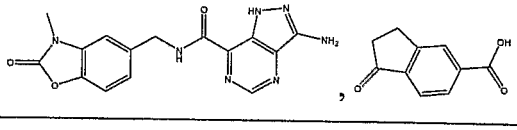
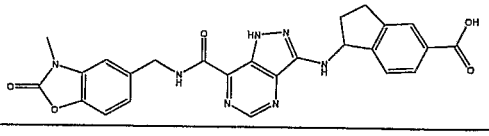
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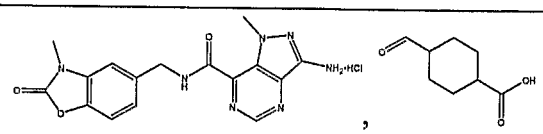
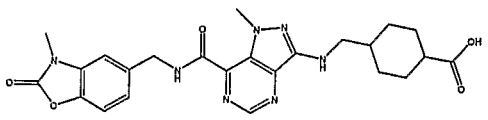
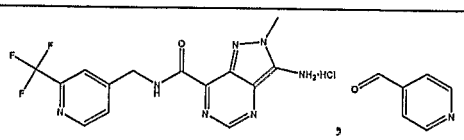
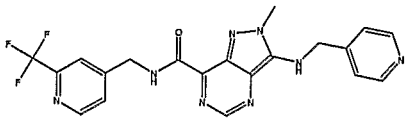
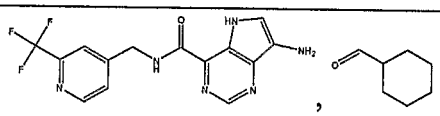
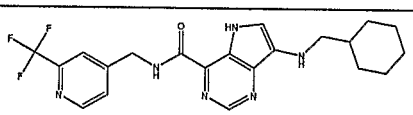
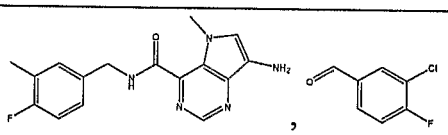
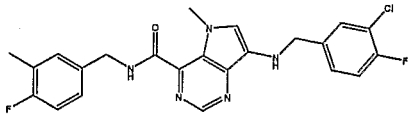
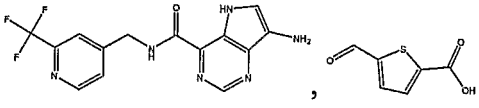
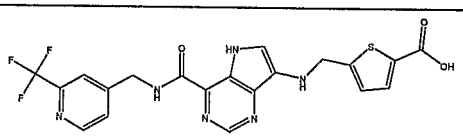
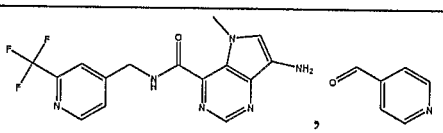
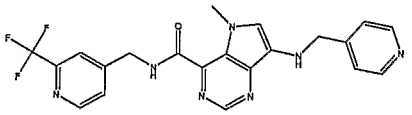
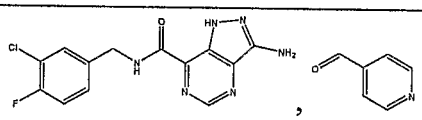
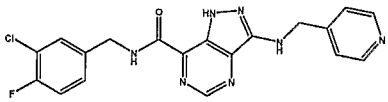
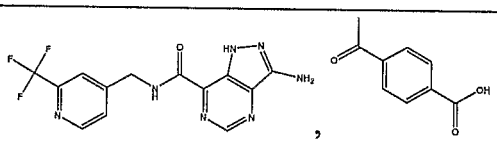
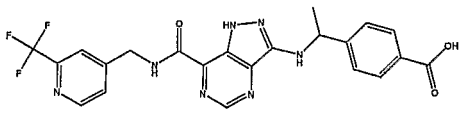
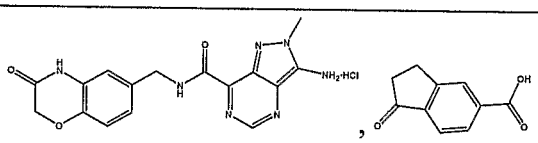
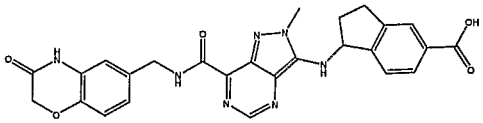
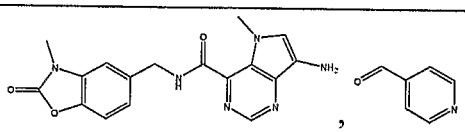
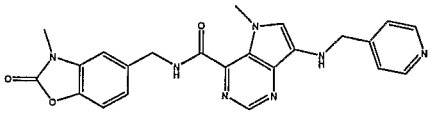
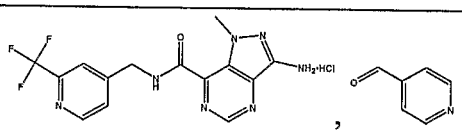
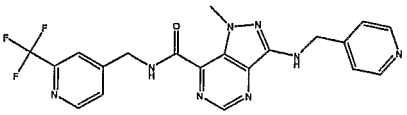
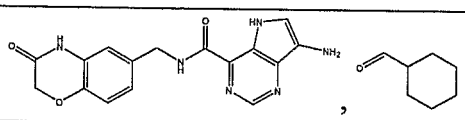
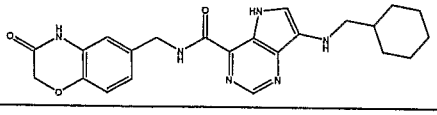
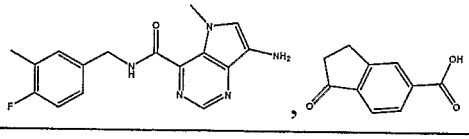
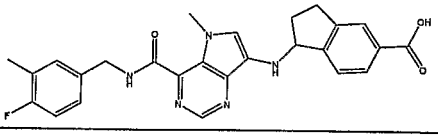
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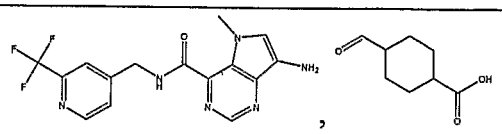
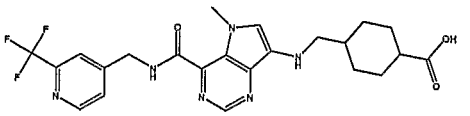
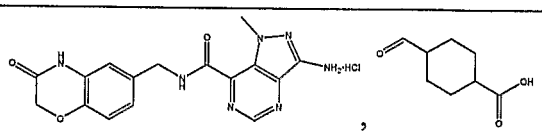
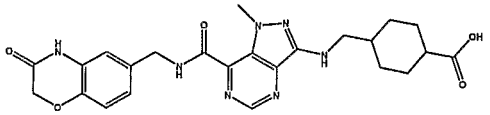
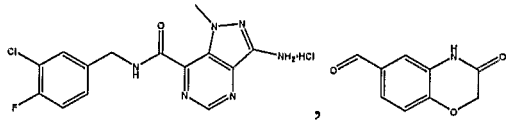
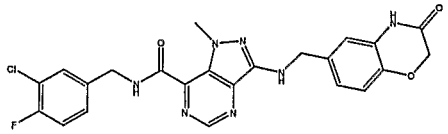
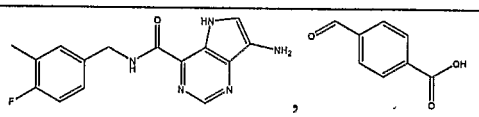
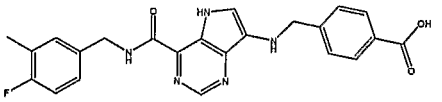
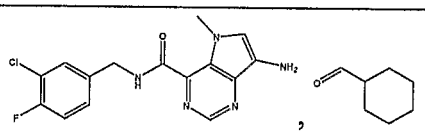
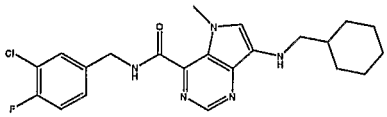
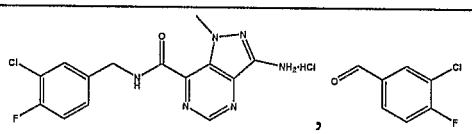
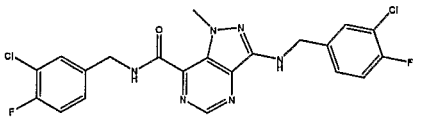
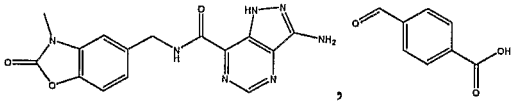
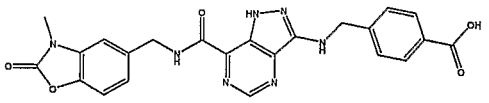
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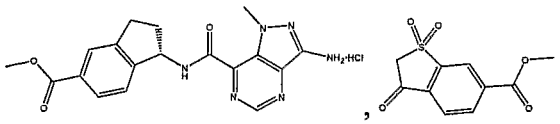
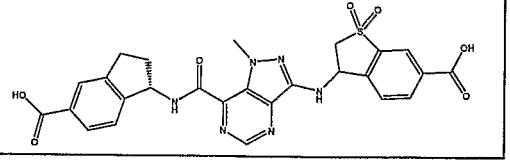
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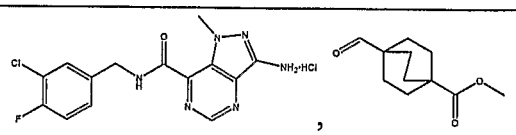
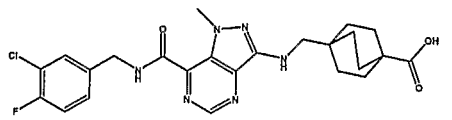
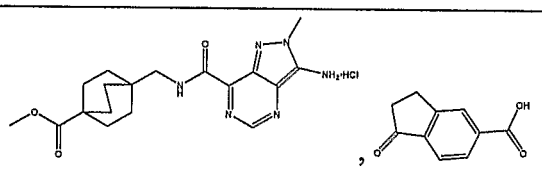
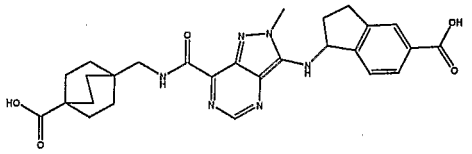
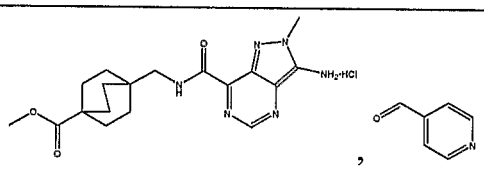
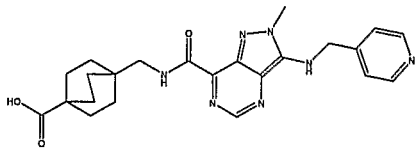
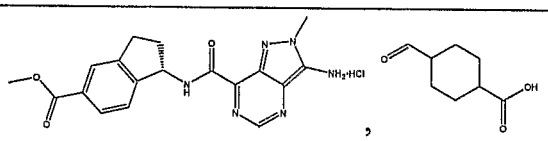
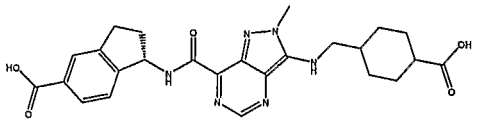
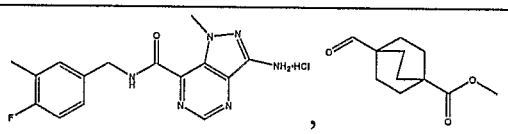
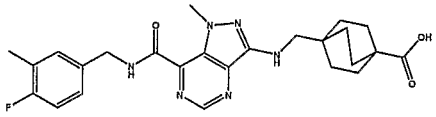
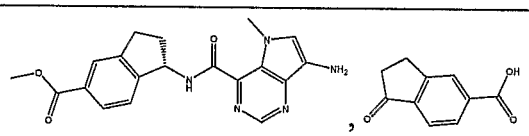
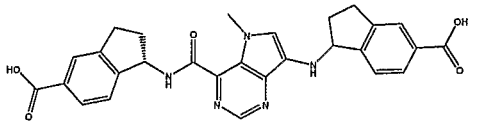
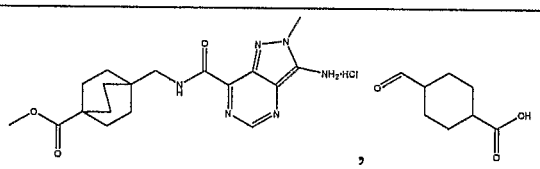
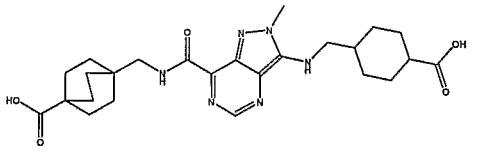
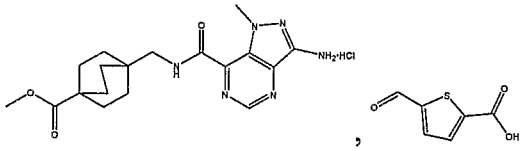
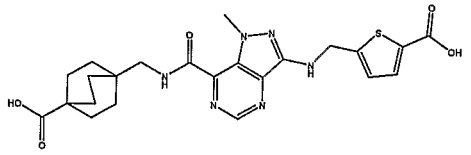
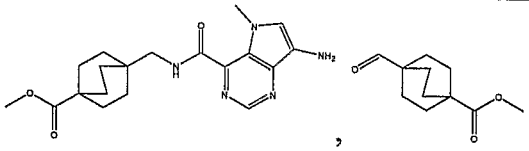
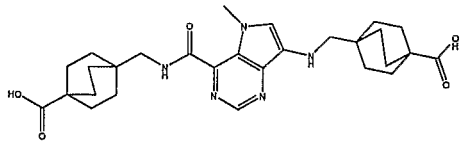
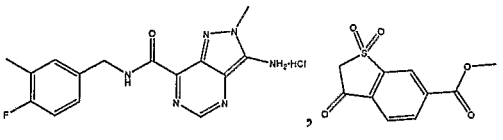
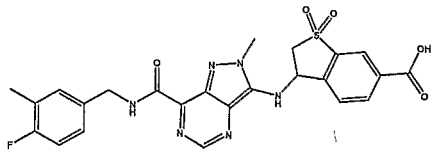
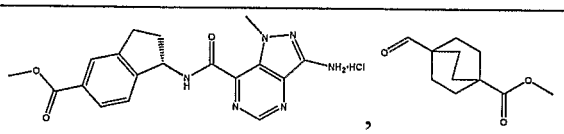
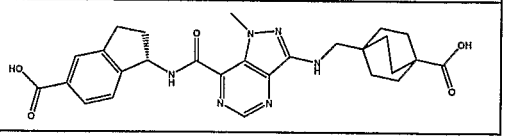
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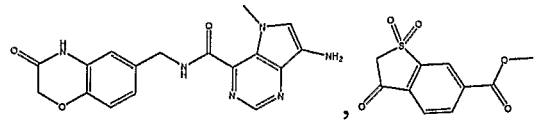
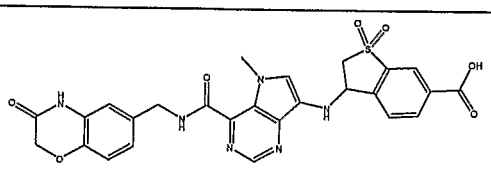
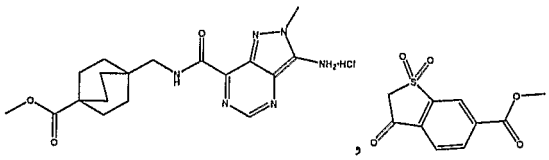
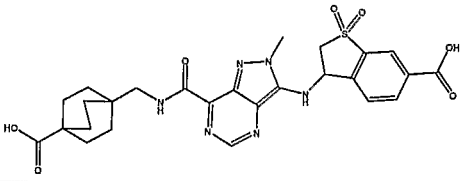
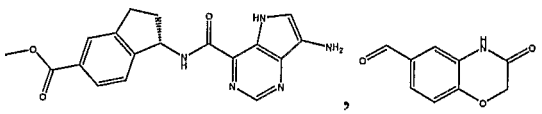
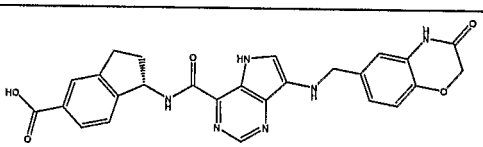
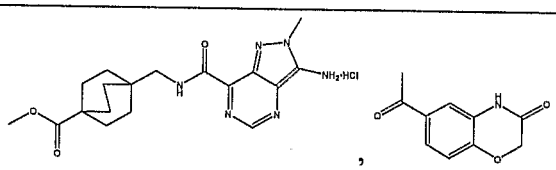
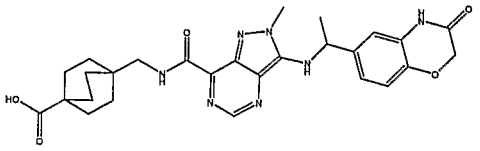
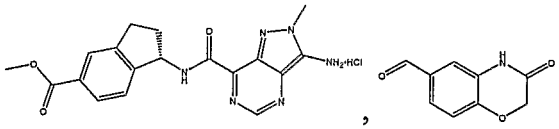
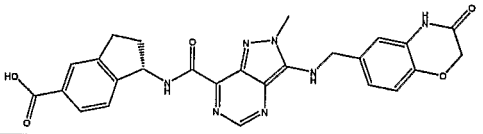
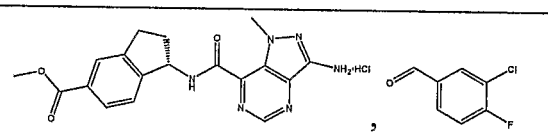
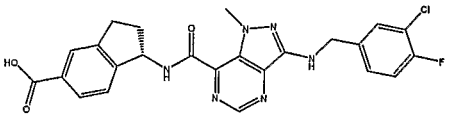
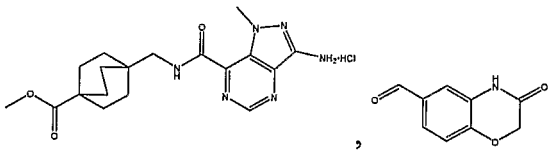
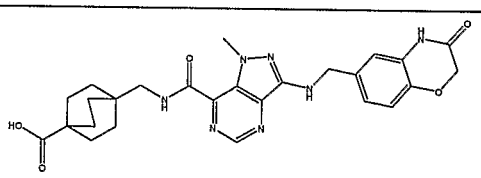
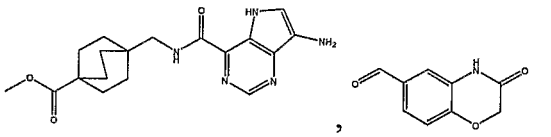
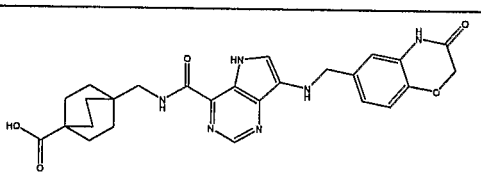
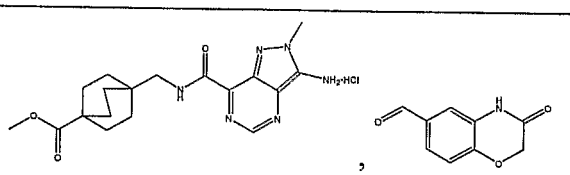
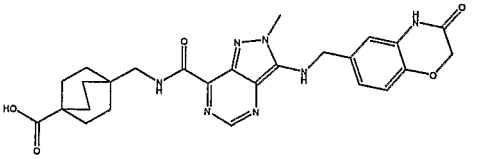
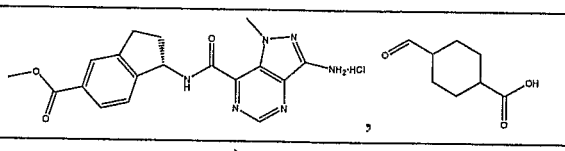
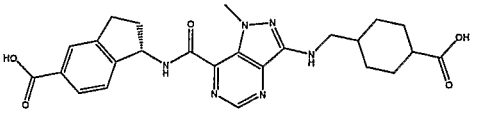
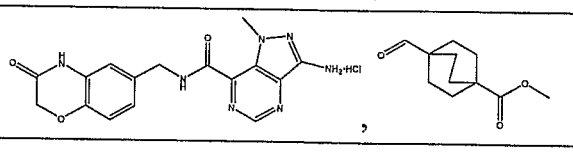
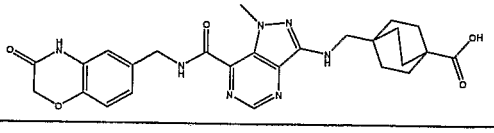
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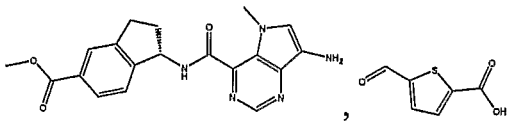
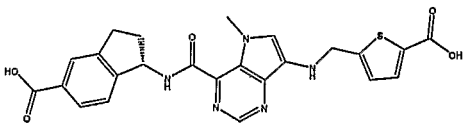
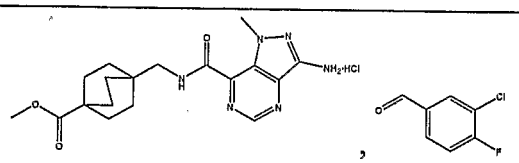
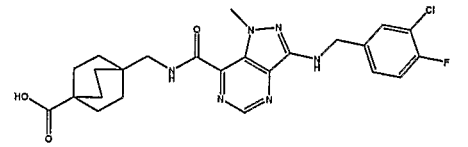
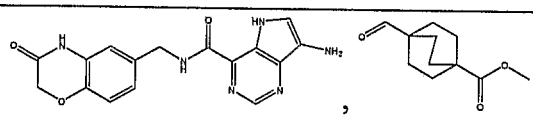
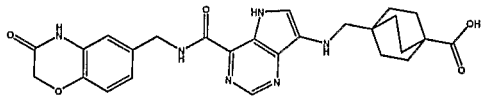
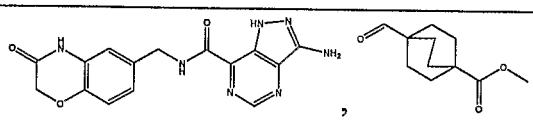
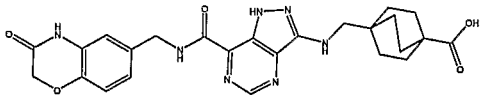
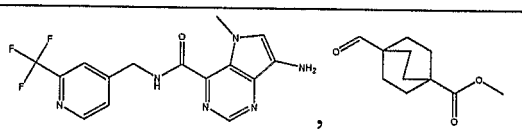
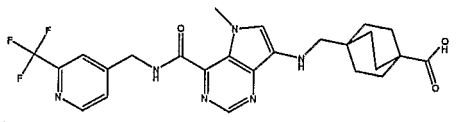
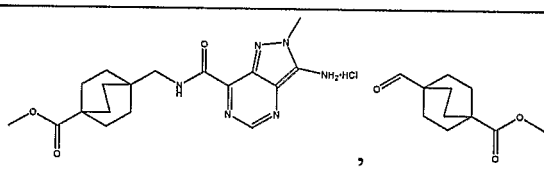
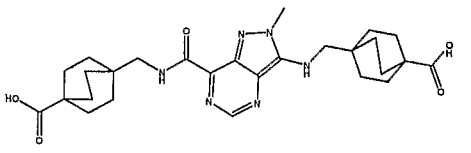
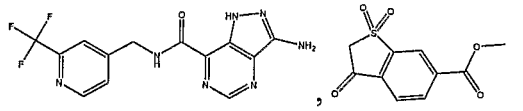
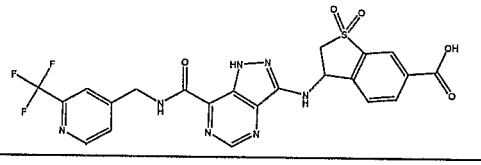
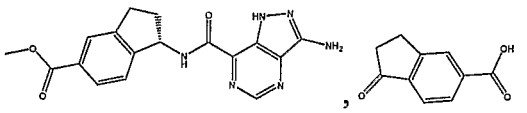
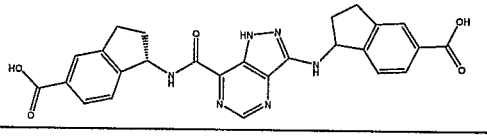
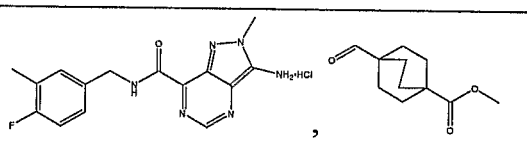
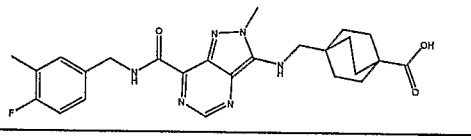
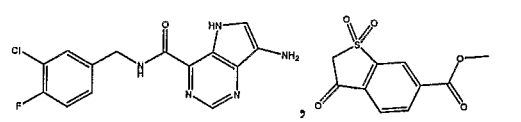
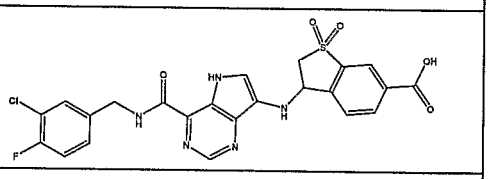
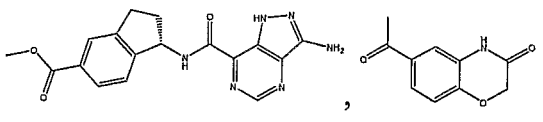
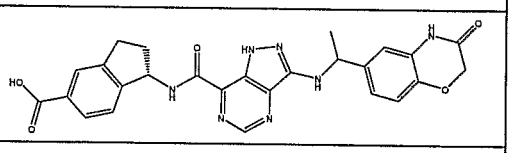
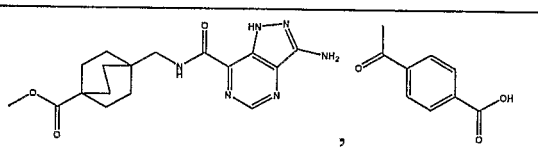
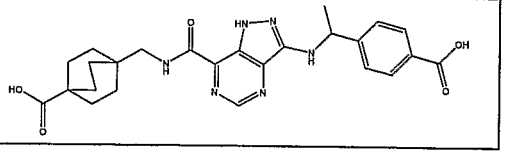
[0613] If one were to follow a similar procedure as described in Example 479, except using the carbonyl compound indicated in Table II-34 below and if one were to treat the obtained esters similarly as described in Example 314 or 315, the following compounds would be obtained.

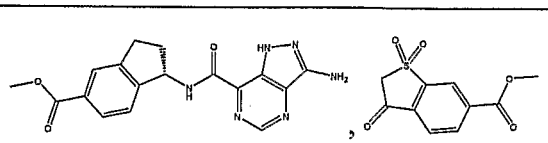
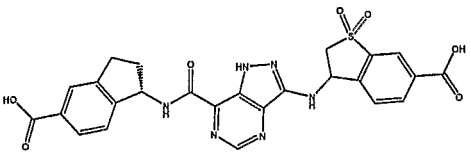
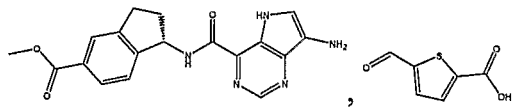
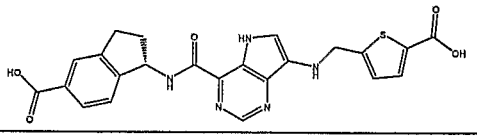
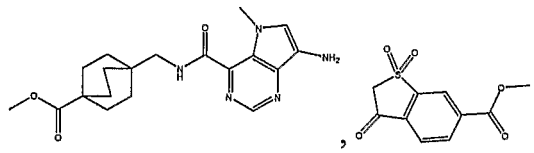
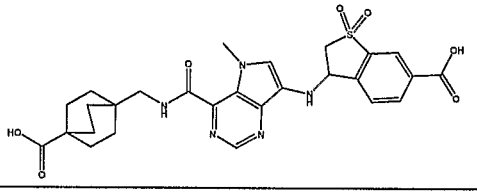
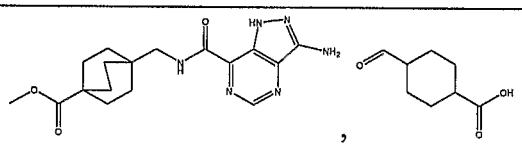
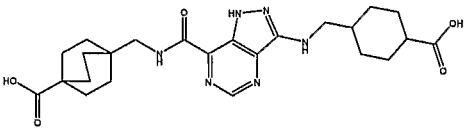
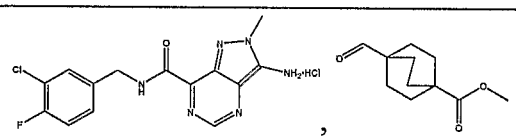
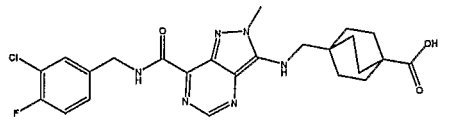
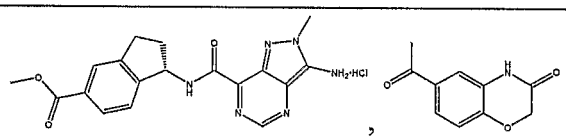
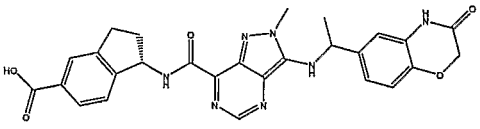
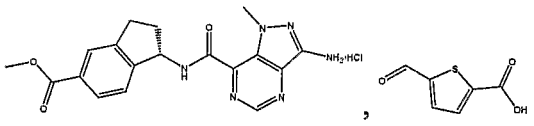
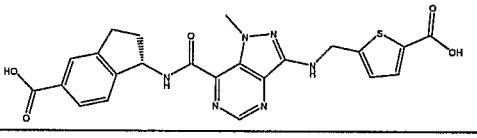
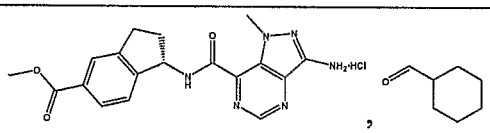
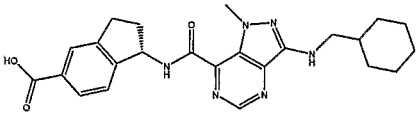
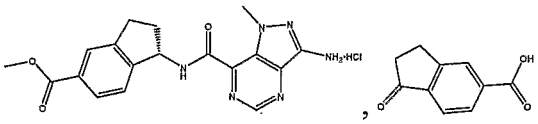
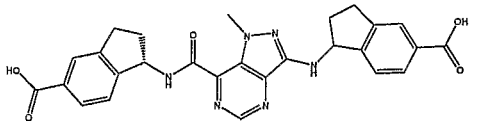
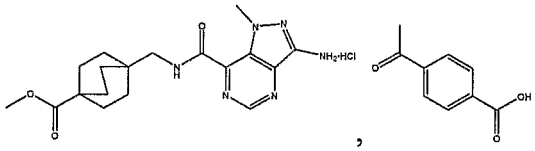
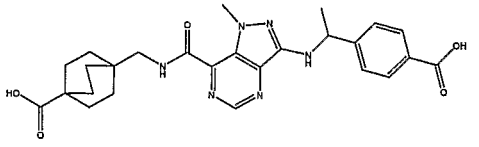
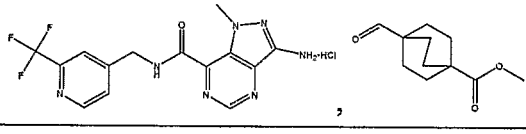
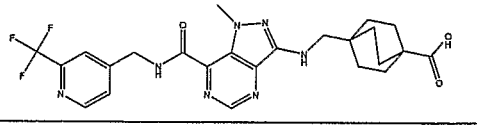
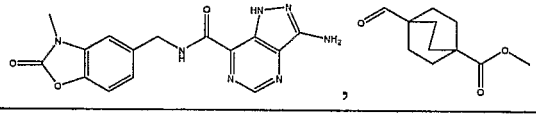
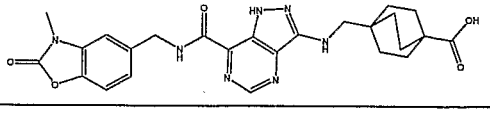
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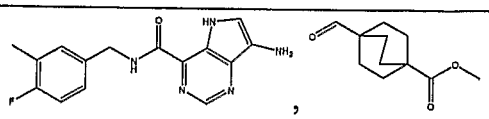
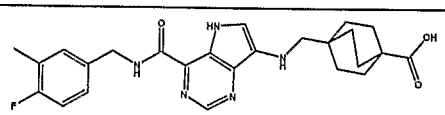
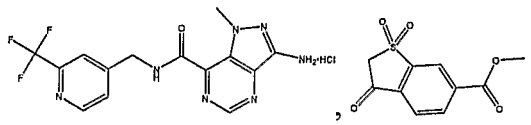
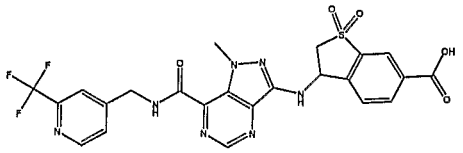
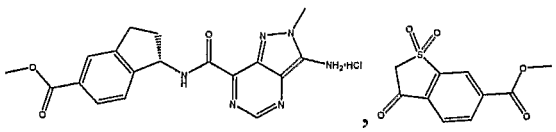
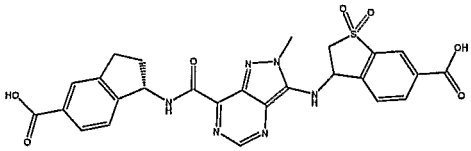
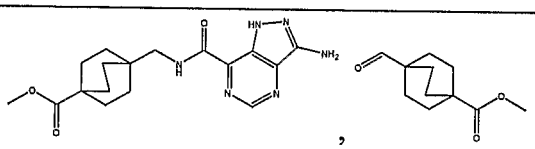
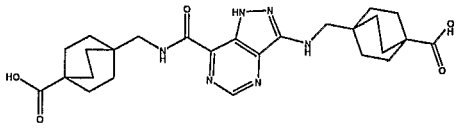
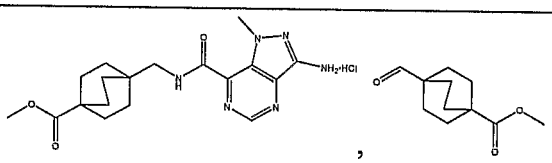
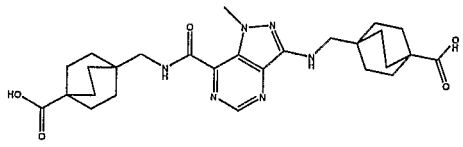
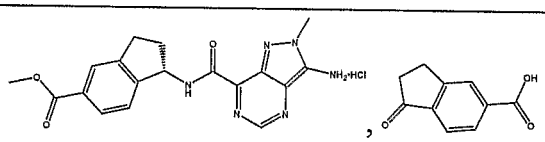
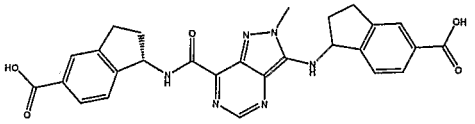
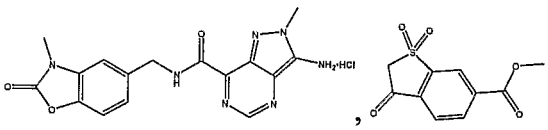
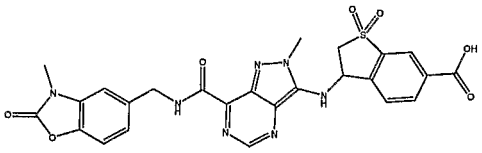
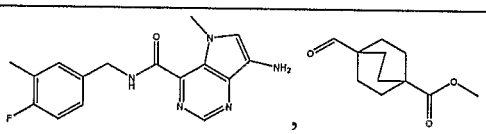
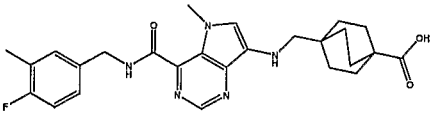
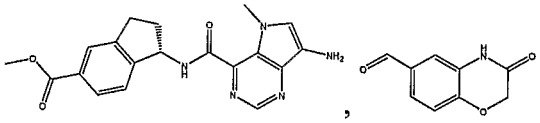
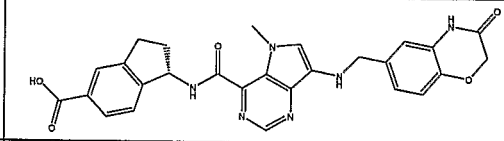
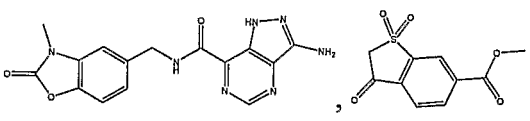
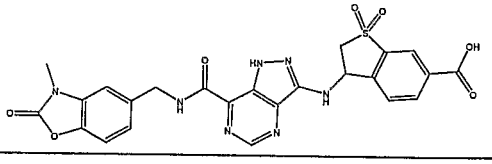
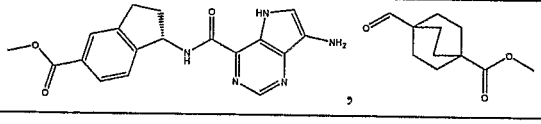
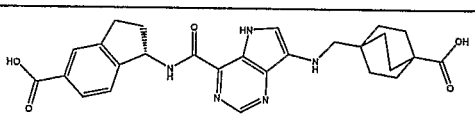
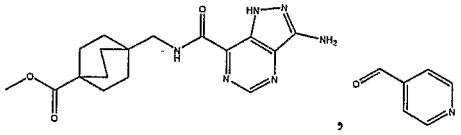
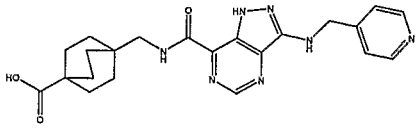
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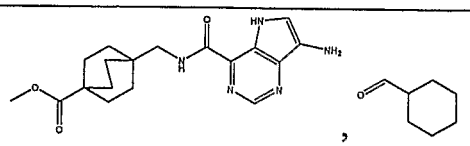
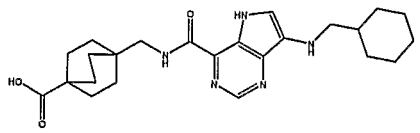
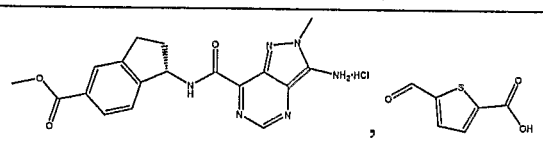
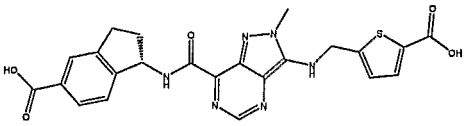
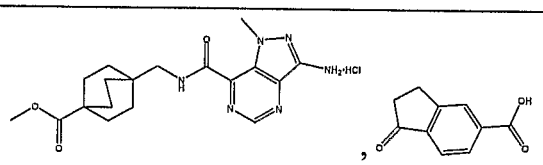
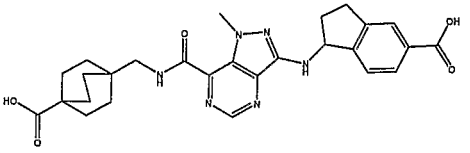
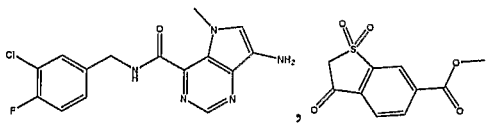
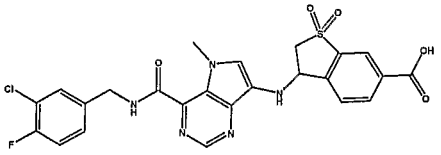
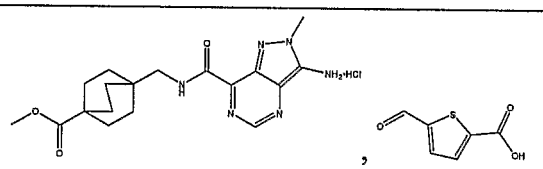
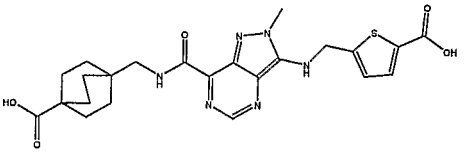
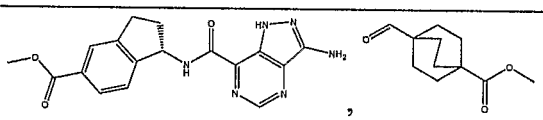
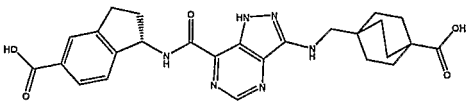
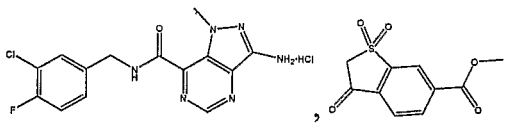
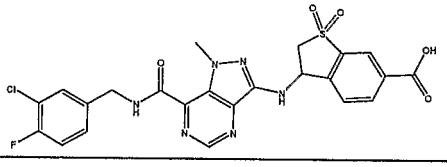
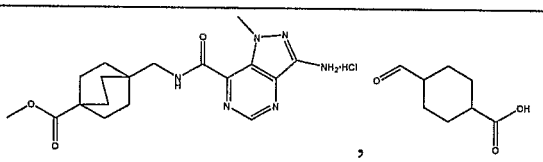
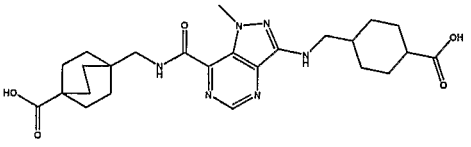
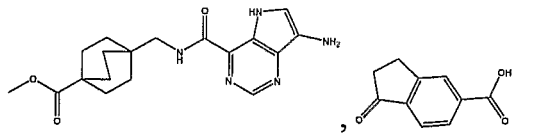
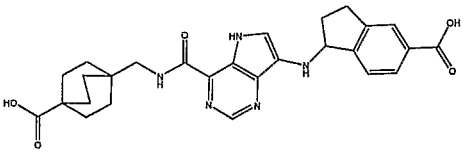
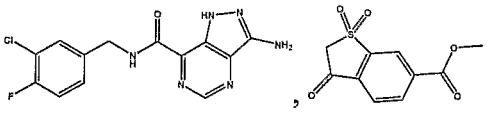
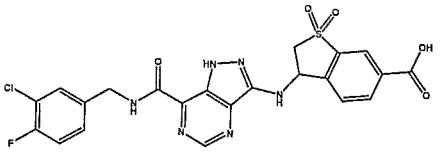
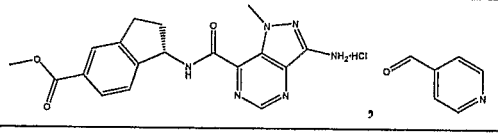
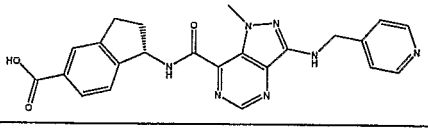
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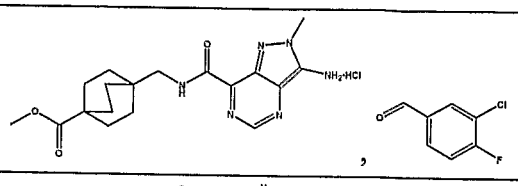
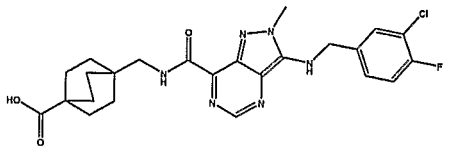
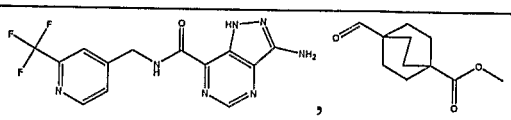
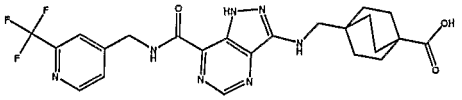
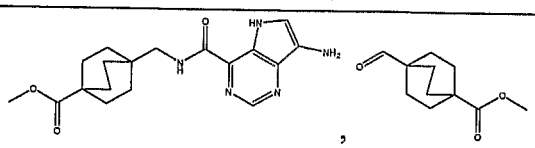
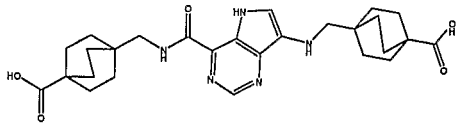
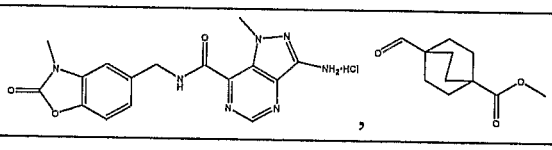
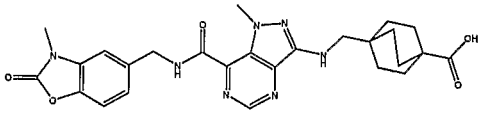
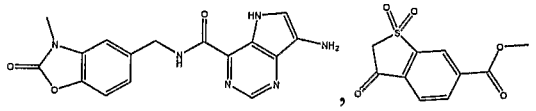
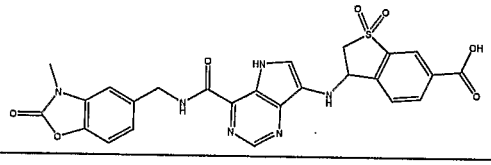
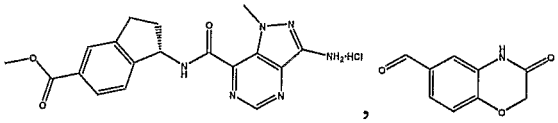
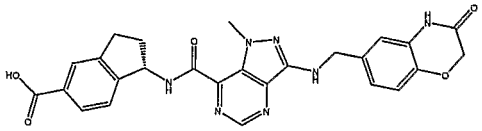
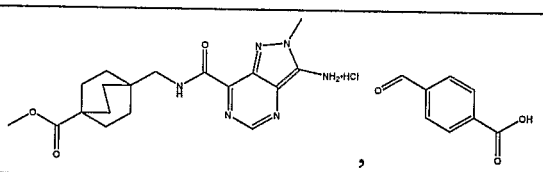
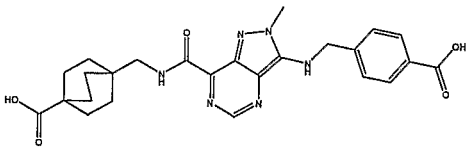
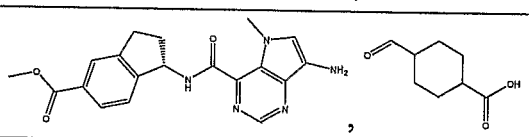
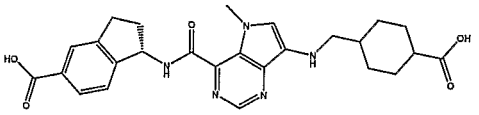
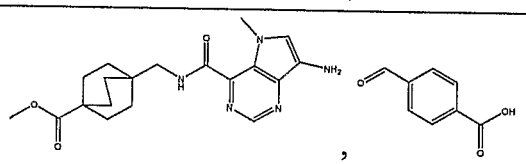
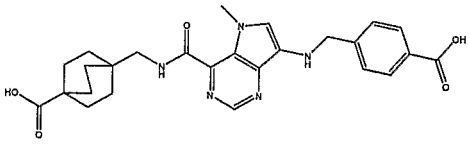
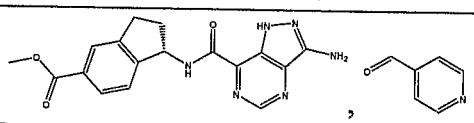
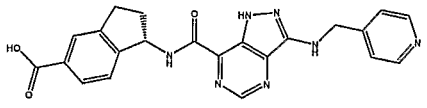
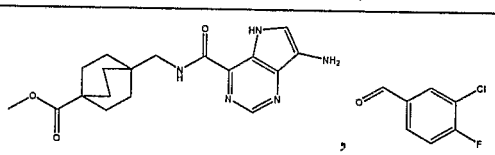
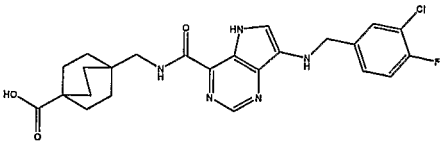
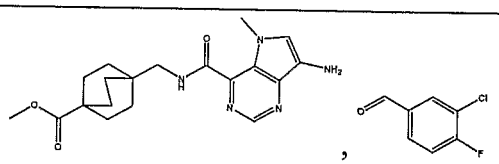
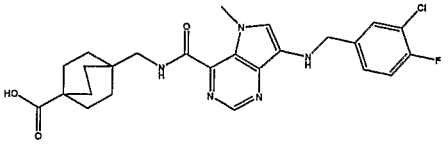
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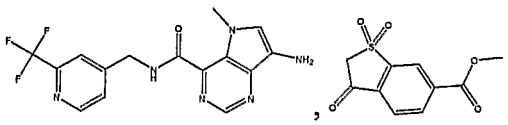
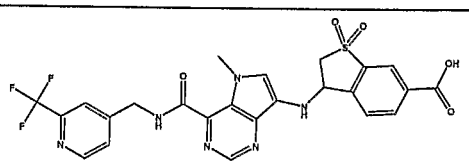
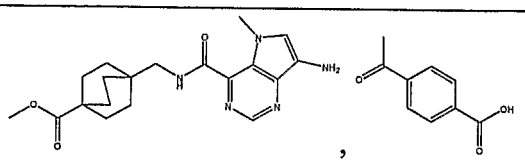
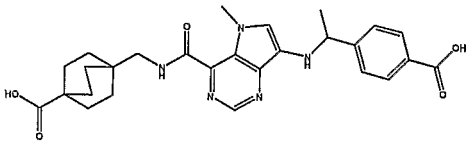
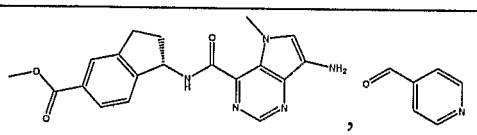
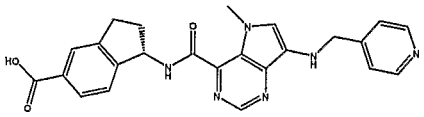
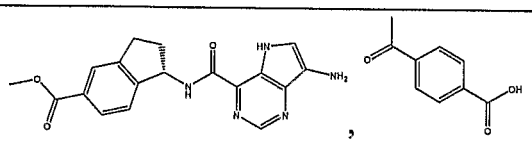
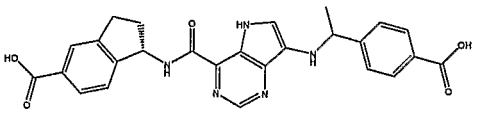
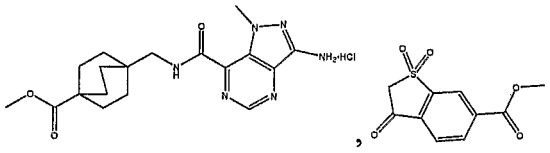
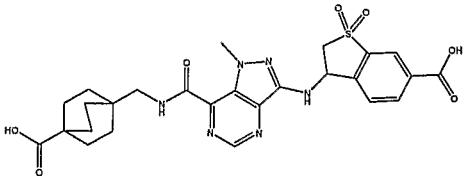
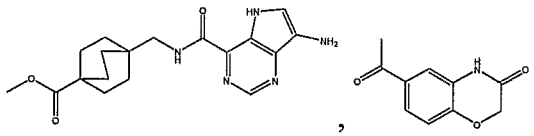
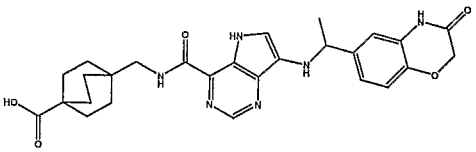
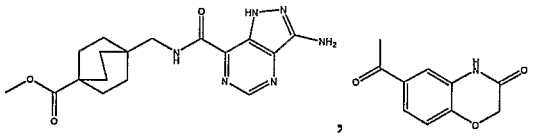
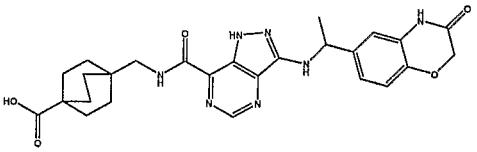
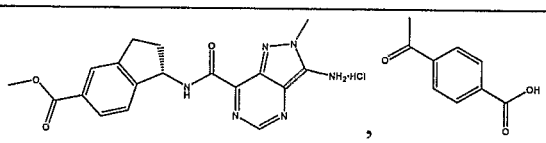
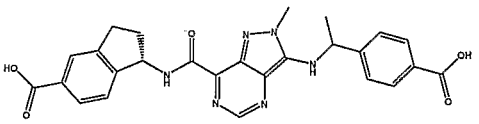
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Ex. #	amine, carbonyl compound	product
1537		
1538		
1539		
1540		
1541		
1542		
1543		
1544		
1545		
1546		
1547		
1548		

Ex. #	amine, carbonyl compound	product
1549		
1550		
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1553		
1554		
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1558		
1559		

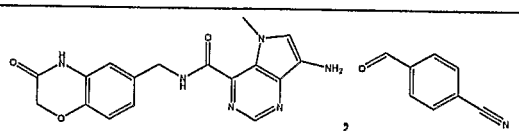
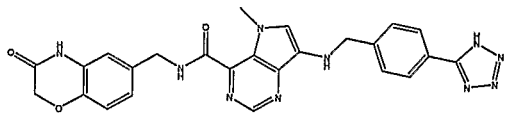
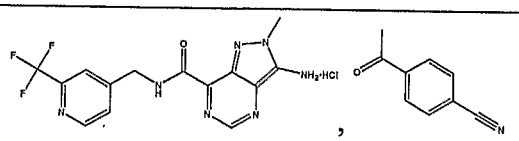
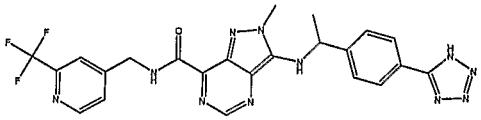
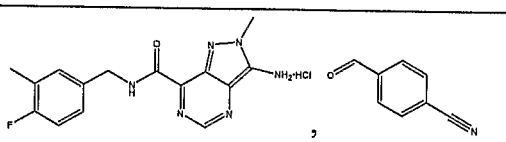
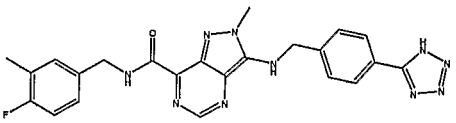
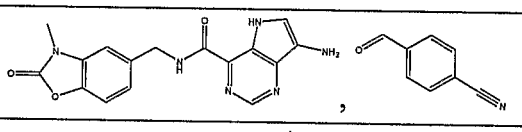
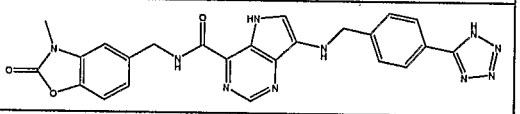
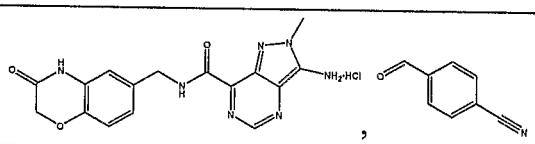
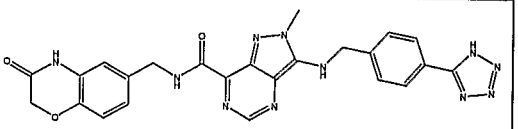
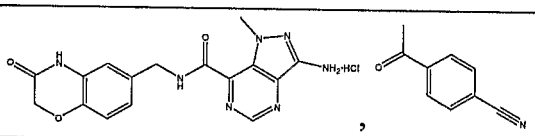
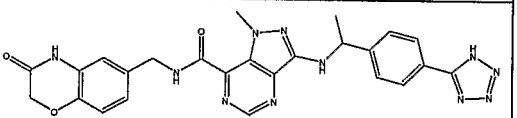
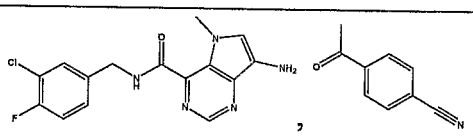
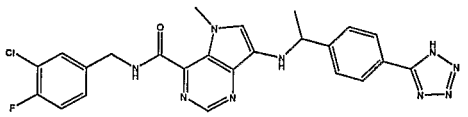
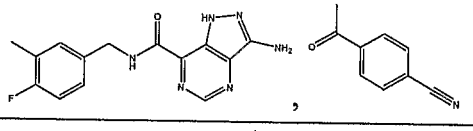
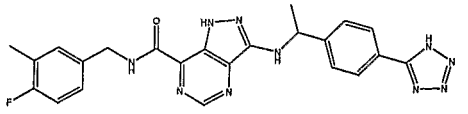
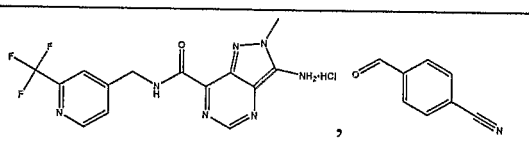
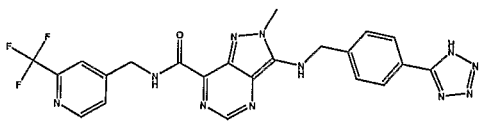
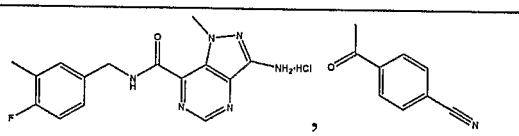
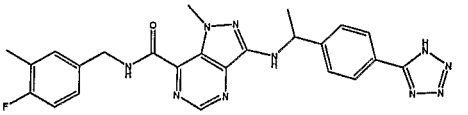
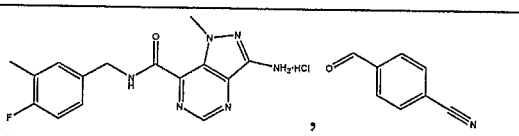
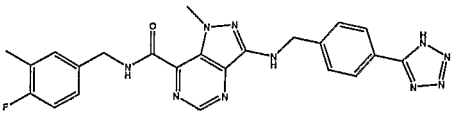
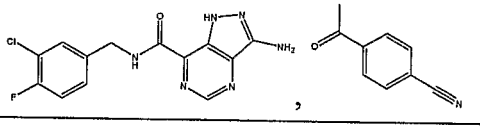
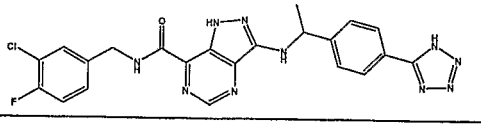
Ex. #	amine, carbonyl compound	product
1560		
1561		
1562		
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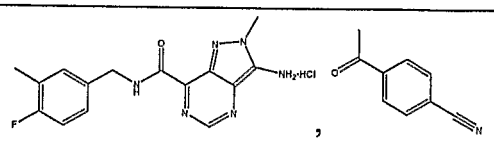
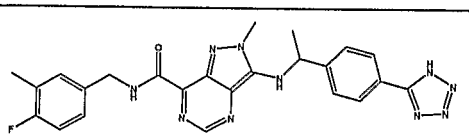
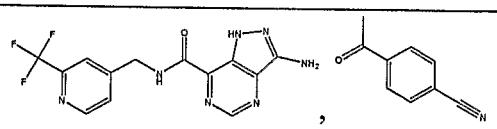
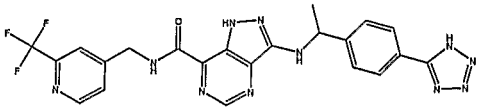
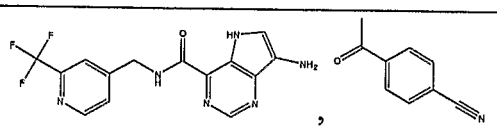
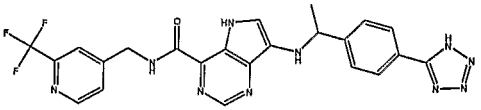
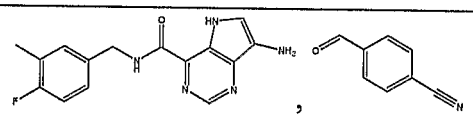
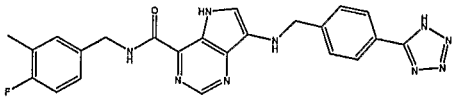
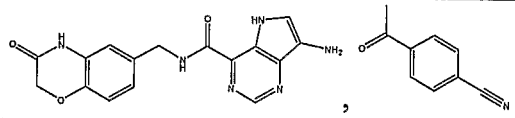
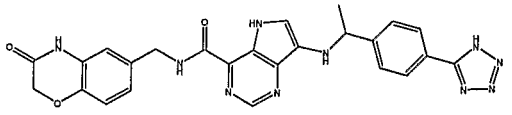
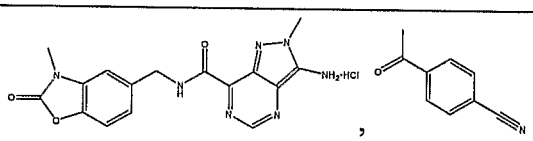
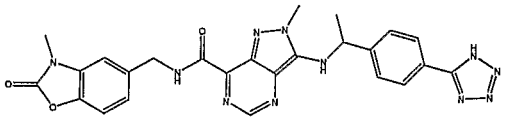
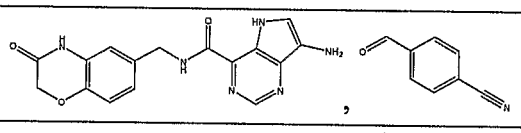
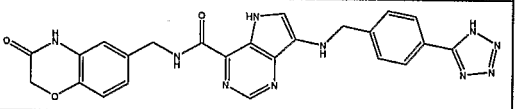
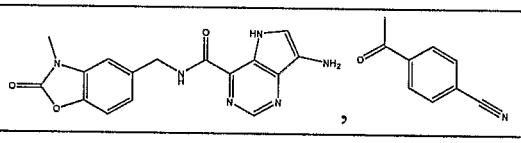
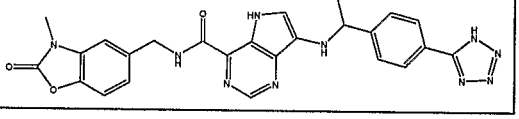
Ex. #	amine, carbonyl compound	product
1572		
1573		
1574		
1575		
1576		
1577		
1578		
1579		

Examples 1580-1599

[0614] If one were to follow a similar procedure as described in Example 479, except using the carbonyl compound indicated in Table II-35 below and if one were to treat the obtained nitriles similarly as described in Example 469, the following compounds would be obtained.

Table II-35

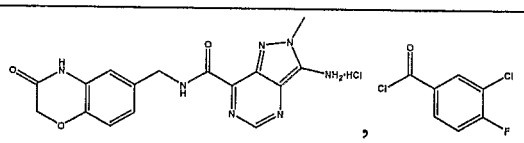
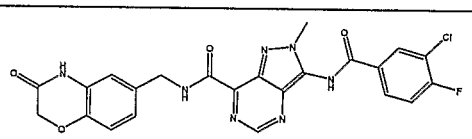
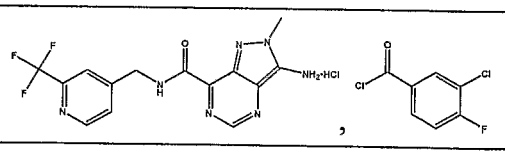
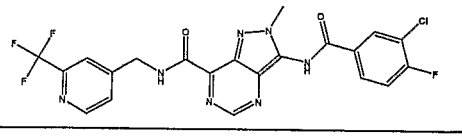
Ex. #	amine, carbonyl compound	product
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1582		
1583		
1584		
1585		
1586		
1587		
1588		
1589		
1590		
1591		

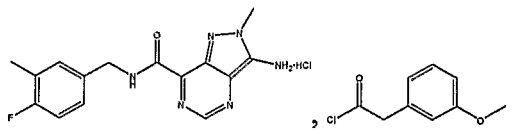
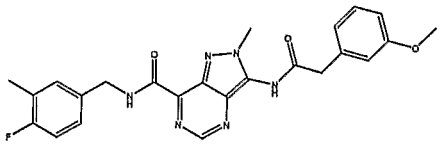
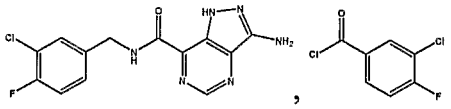
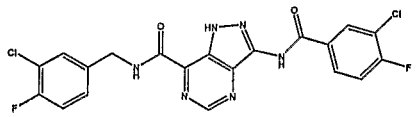
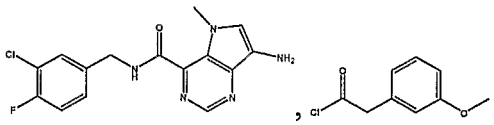
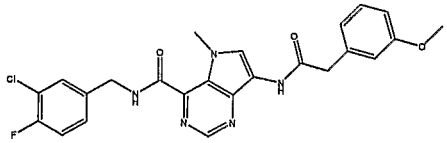
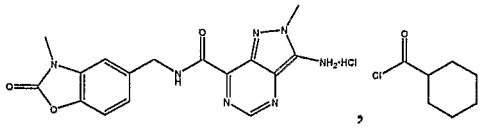
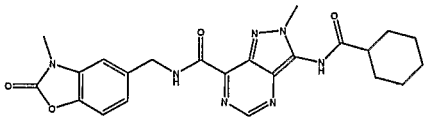
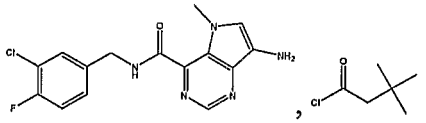
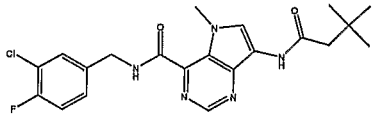
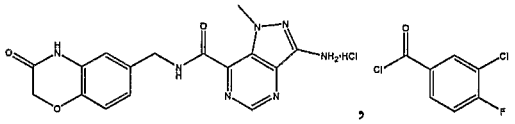
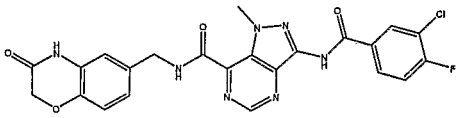
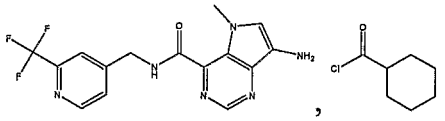
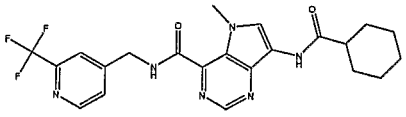
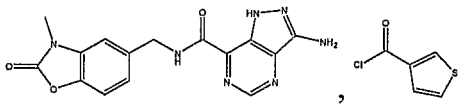
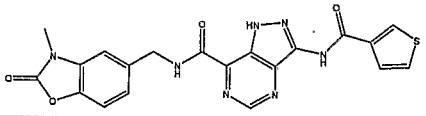
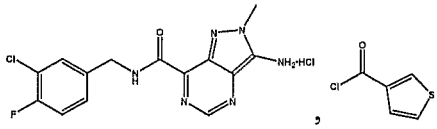
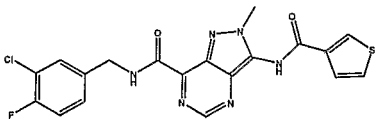
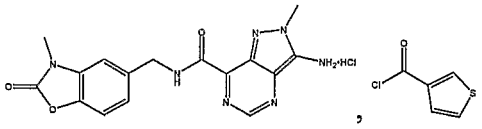
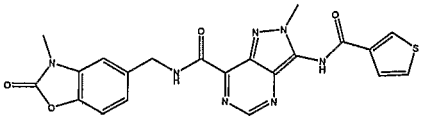
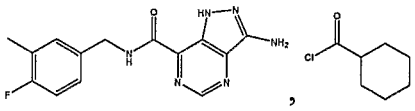
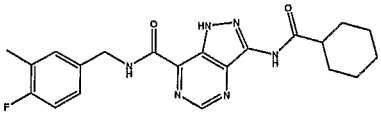
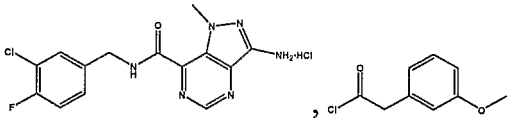
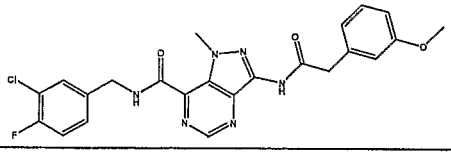
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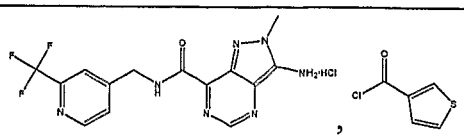
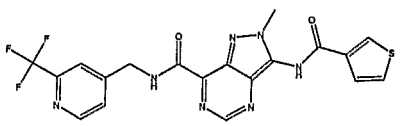
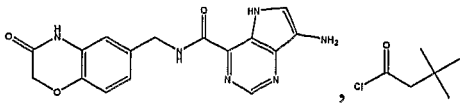
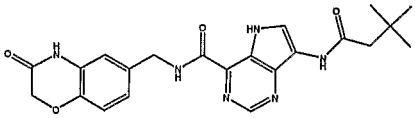
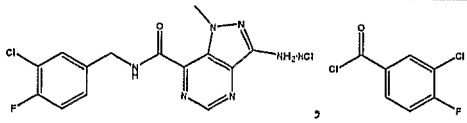
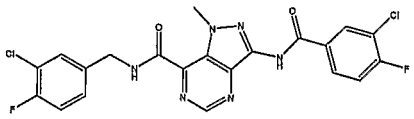
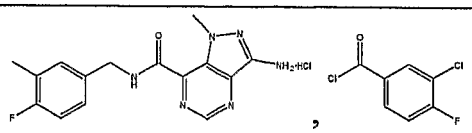
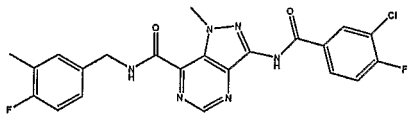
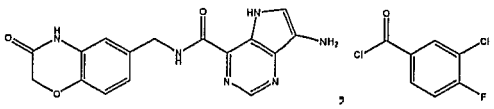
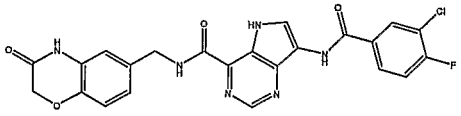
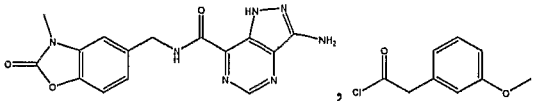
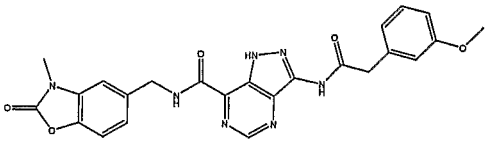
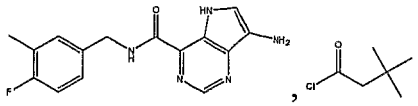
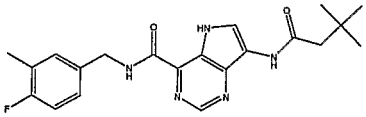
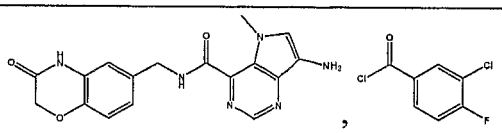
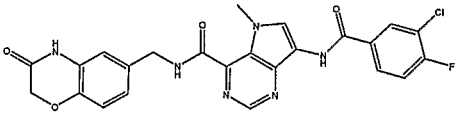
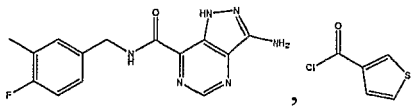
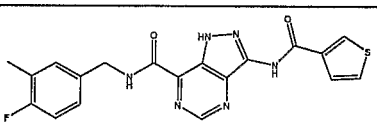
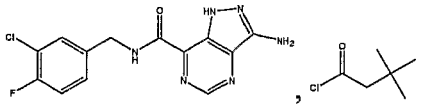
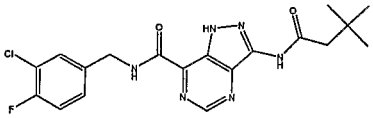
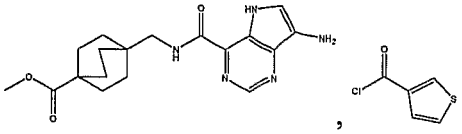
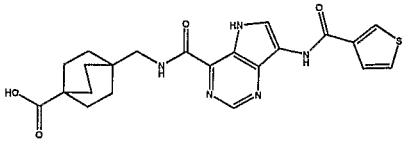
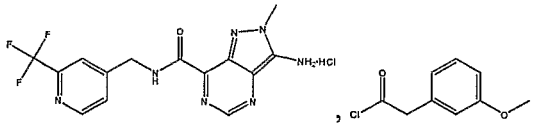
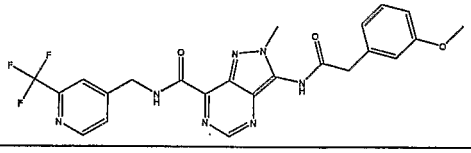
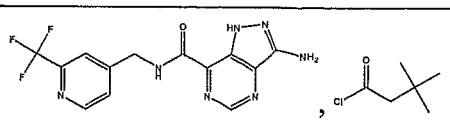
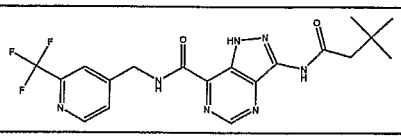
Examples 1600-1649

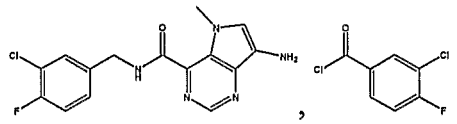
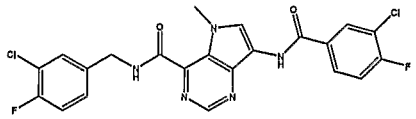
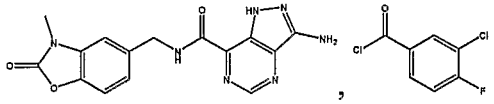
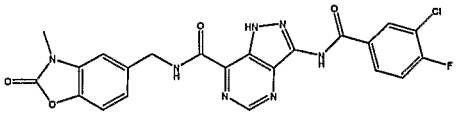
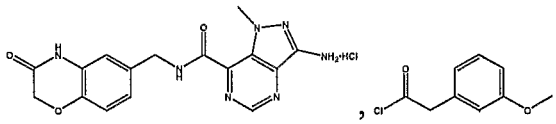
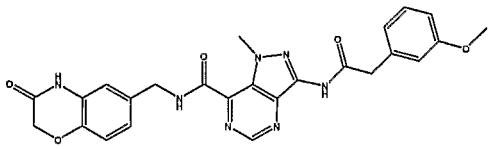
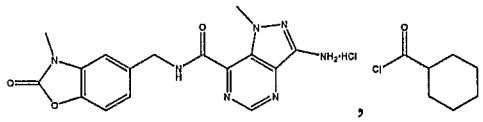
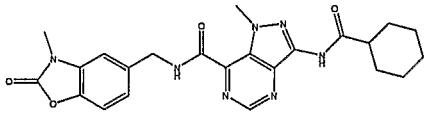
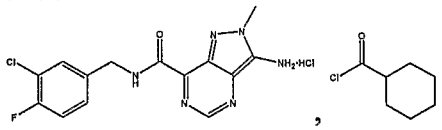
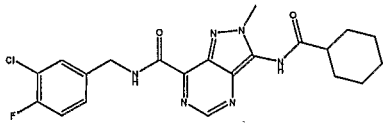
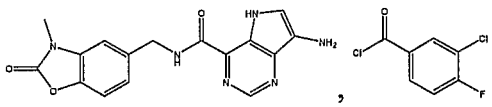
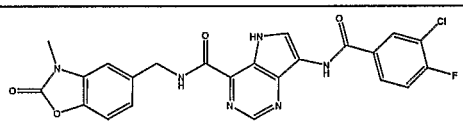
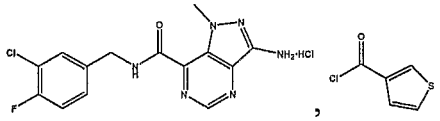
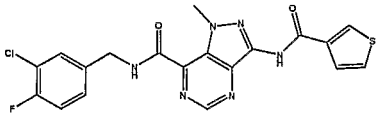
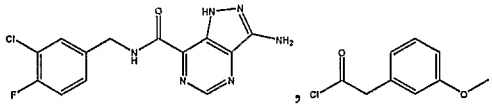
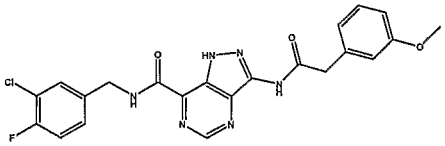
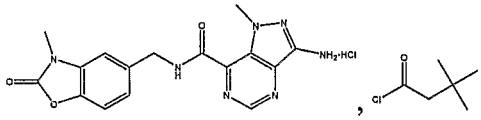
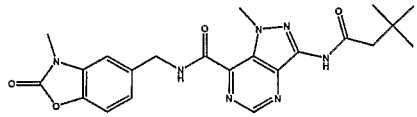
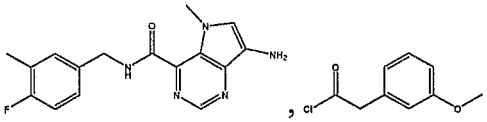
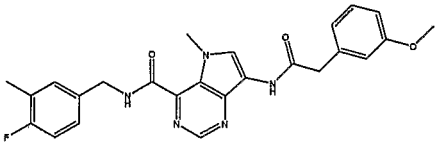
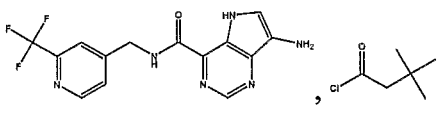
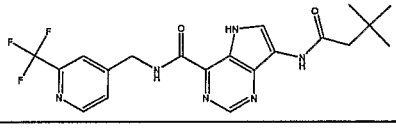
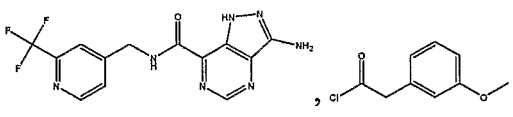
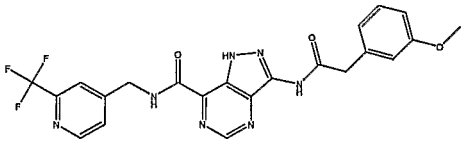
[0615] If one were to follow a similar procedure as described in Example 299, except using the acid chlorides indicated in Table II-36 below, the following compounds would be obtained.

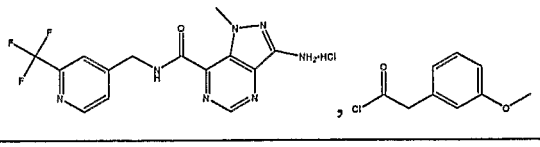
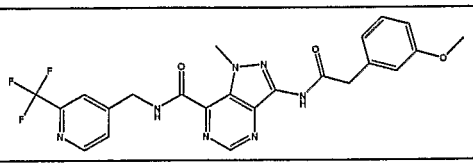
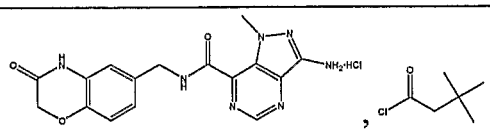
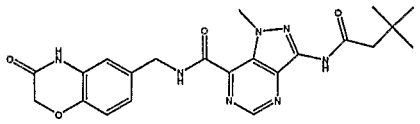
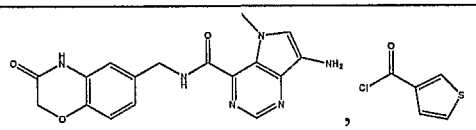
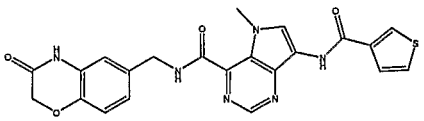
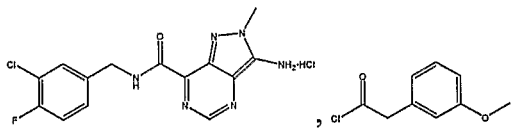
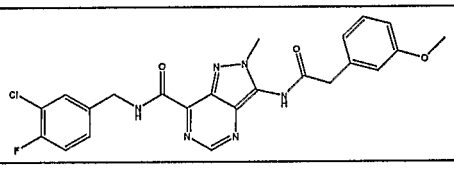
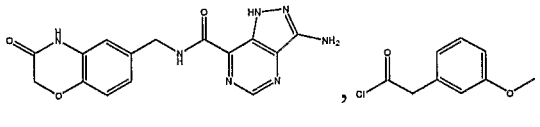
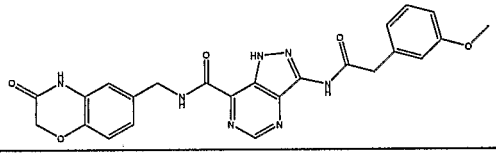
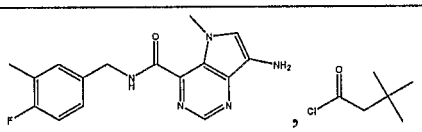
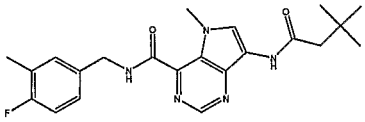
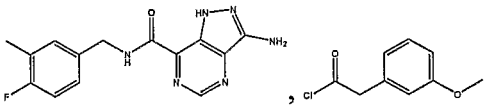
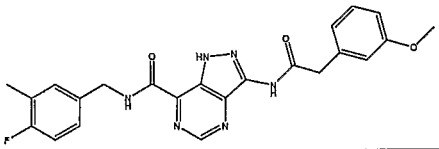
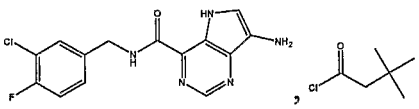
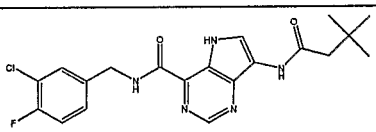
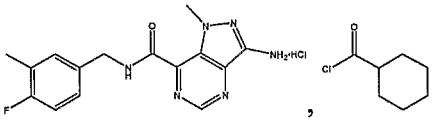
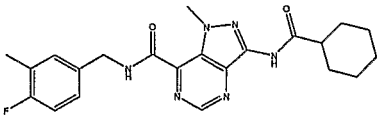
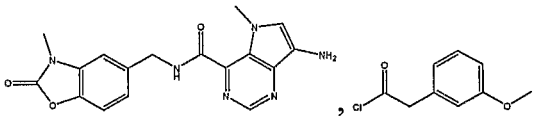
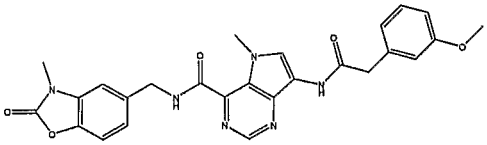
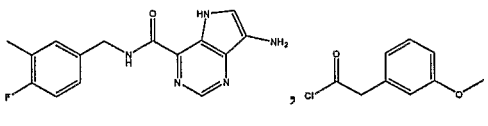
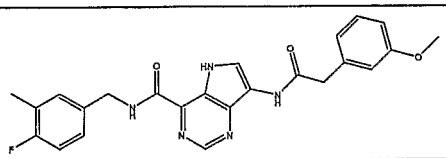
Table II-36

Ex. #	amine, acid chloride	product
1600		
1601		

Ex. #	amine, acid chloride	product
1602		
1603		
1604		
1605		
1606		
1607		
1608		
1609		
1610		
1611		
1612		
1613		

Ex. #	amine, acid chloride	product
1614		
1615		
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1617		
1618		
1619		
1620		
1621		
1622		
1623		
1624		
1625		
1626		

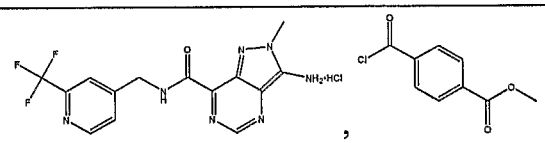
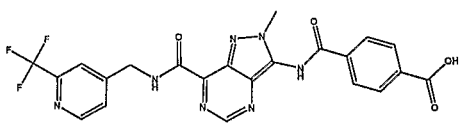
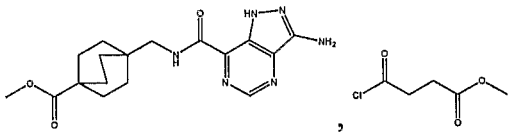
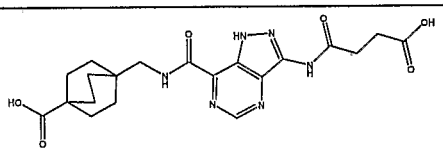
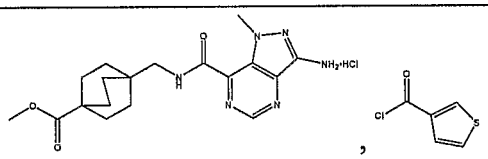
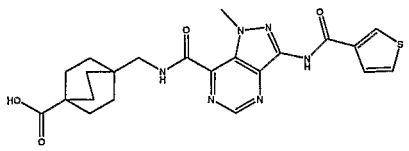
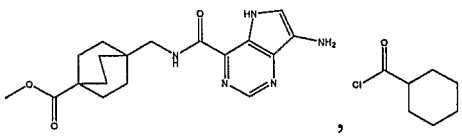
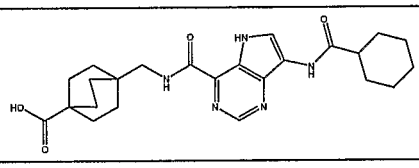
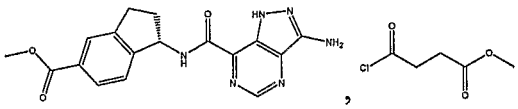
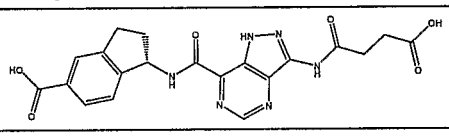
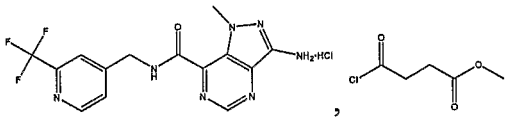
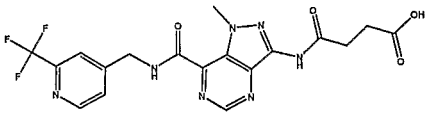
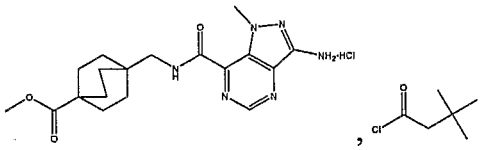
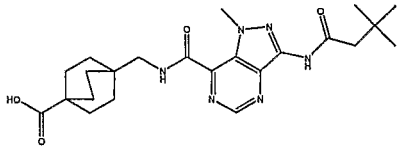
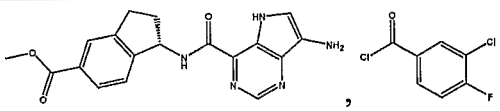
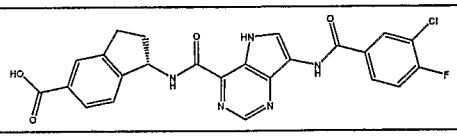
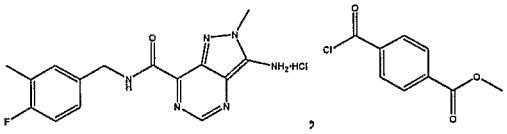
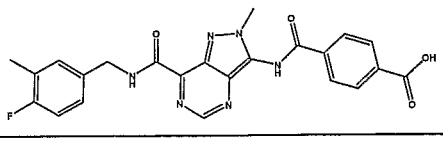
Ex. #	amine, acid chloride	product
1627		
1628		
1629		
1630		
1631		
1632		
1633		
1634		
1635		
1636		
1637		
1638		

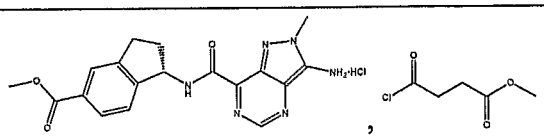
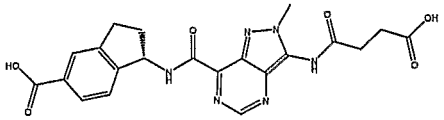
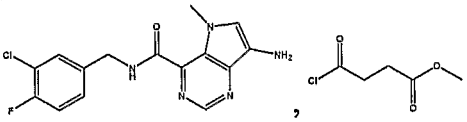
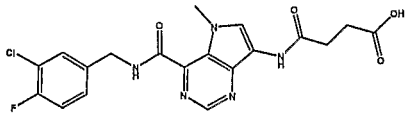
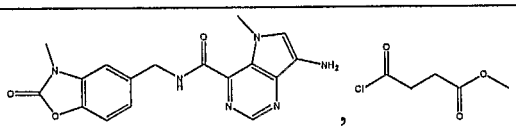
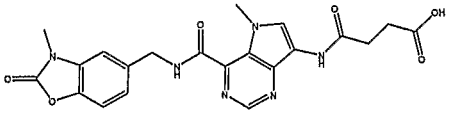
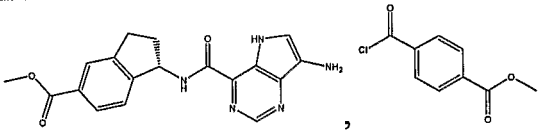
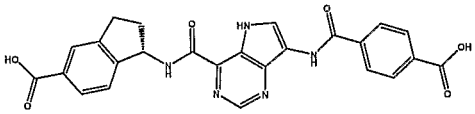
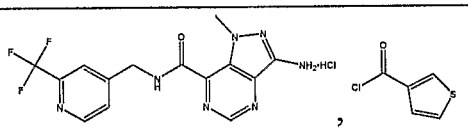
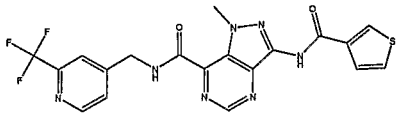
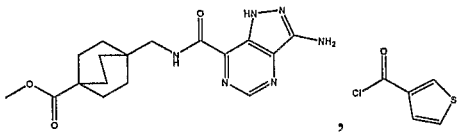
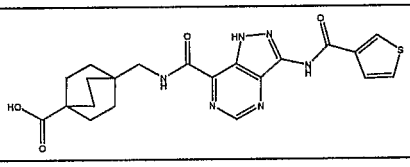
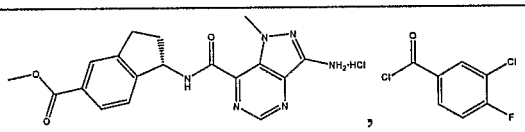
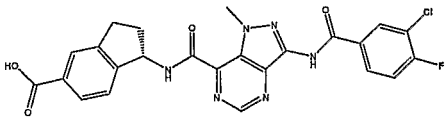
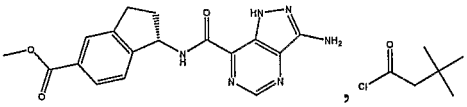
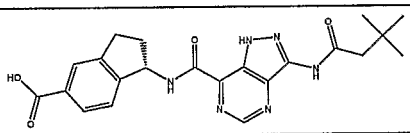
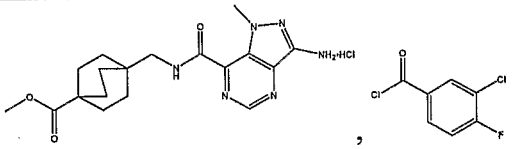
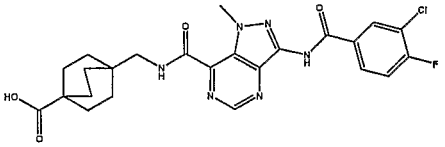
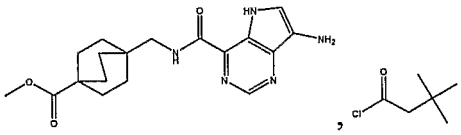
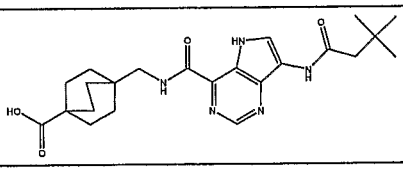
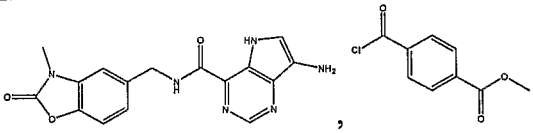
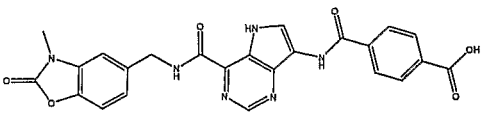
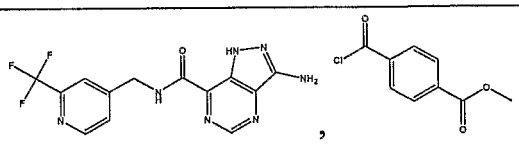
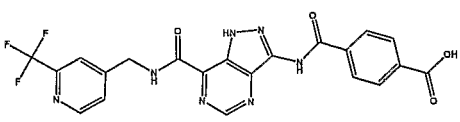
Ex. #	amine, acid chloride	product
1639		
1640		
1641		
1642		
1643		
1644		
1645		
1646		
1647		
1648		
1649		

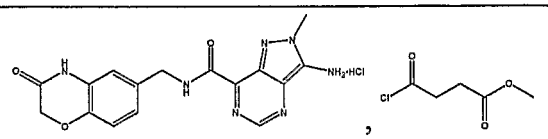
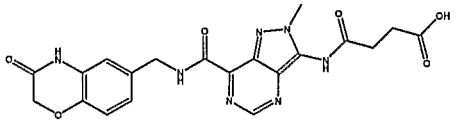
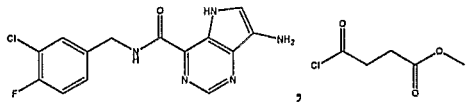
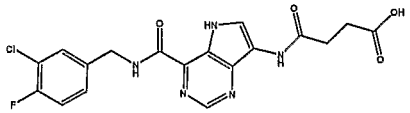
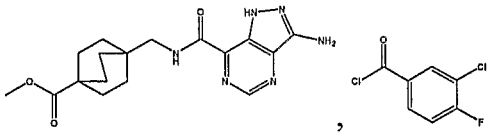
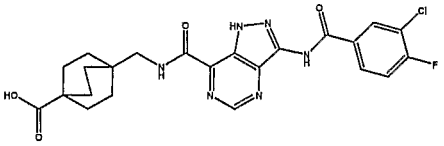
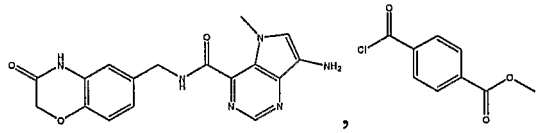
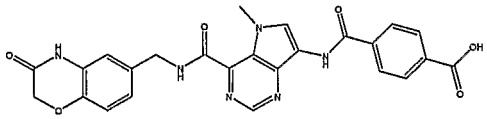
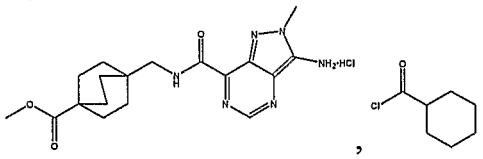
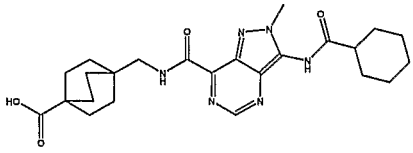
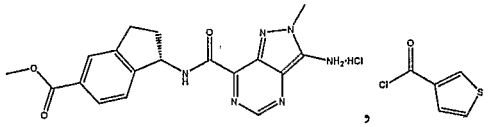
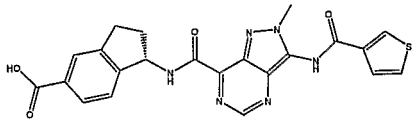
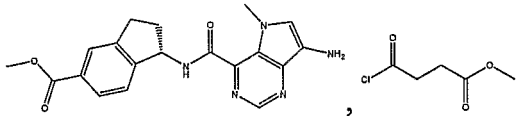
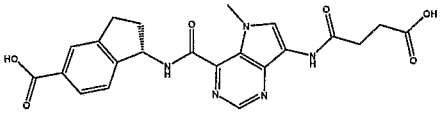
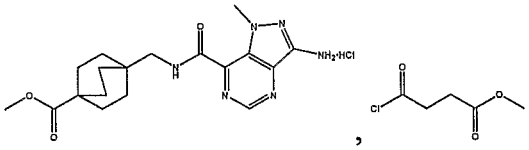
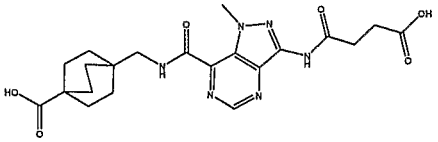
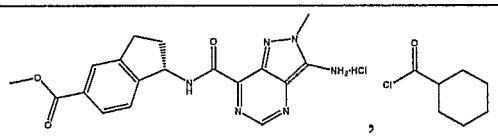
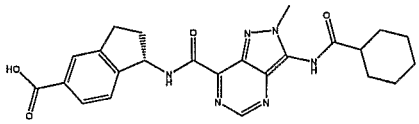
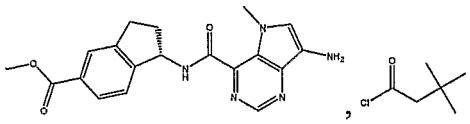
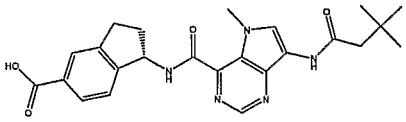
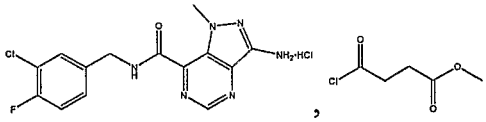
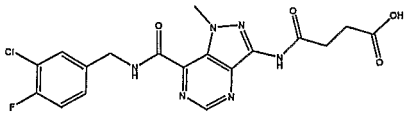
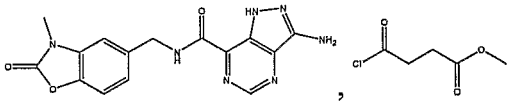
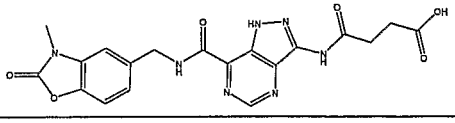
Examples 1650-1689

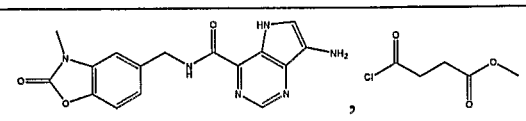
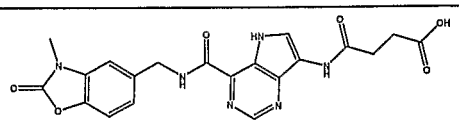
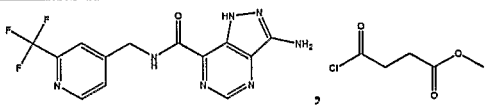
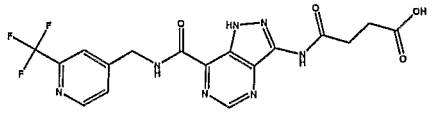
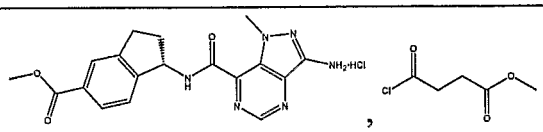
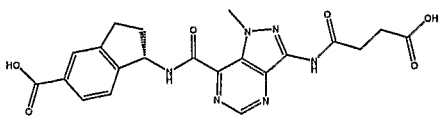
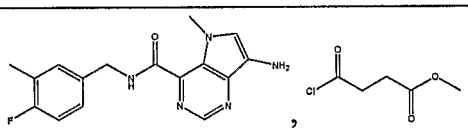
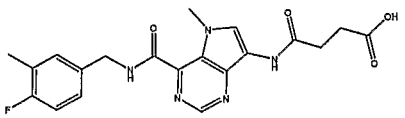
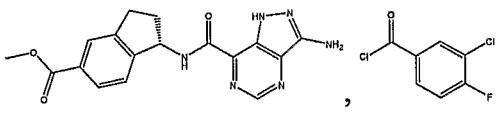
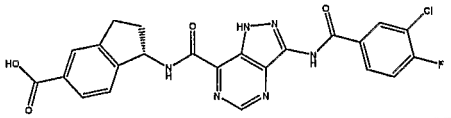
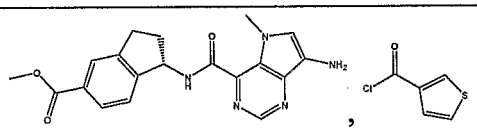
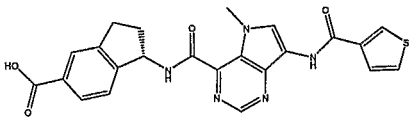
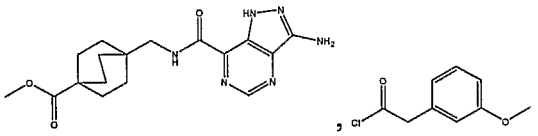
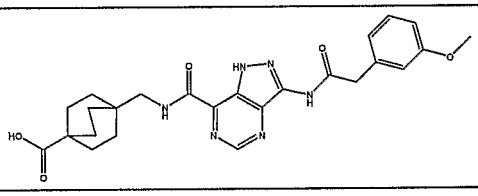
[0616] If one were to follow a similar procedure as described in Example 299, except using the acid chlorides indicated in Table II-37 below and if one were to treat the obtained esters similarly as described in Example 314 or 315, the following compounds would be obtained.

Table II-37

Ex. #	amine, acid chloride	product
1650		
1651		
1652		
1653		
1654		
1655		
1656		
1657		
1658		

Ex. #	amine, acid chloride	product
1659		
1660		
1661		
1662		
1663		
1664		
1665		
1666		
1667		
1668		
1669		
1670		

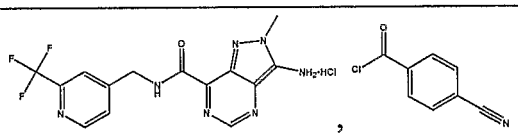
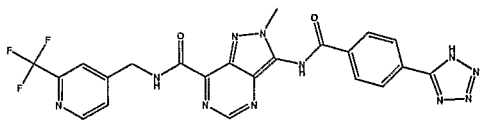
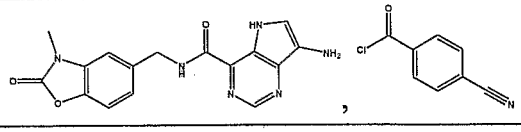
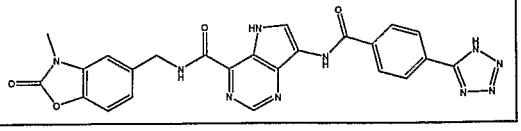
Ex. #	amine, acid chloride	product
1671		
1672		
1673		
1674		
1675		
1676		
1677		
1678		
1679		
1680		
1681		
1682		

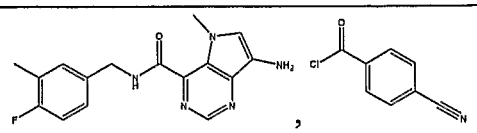
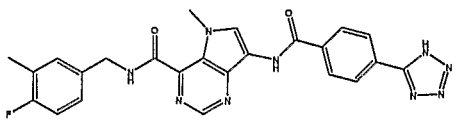
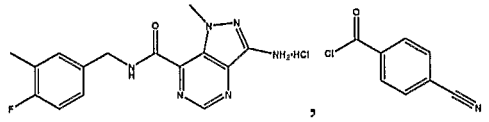
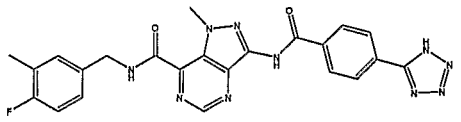
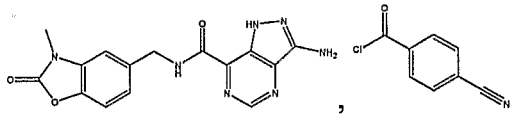
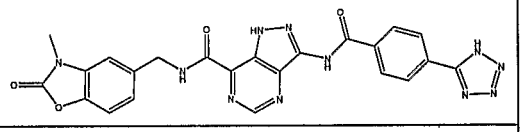
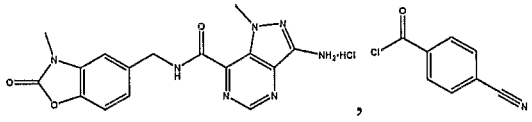
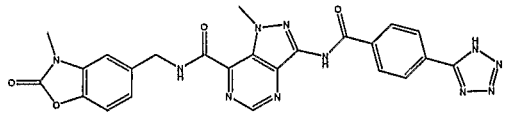
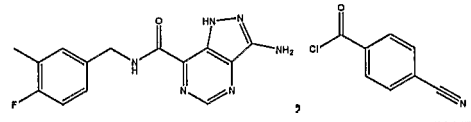
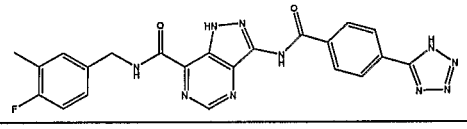
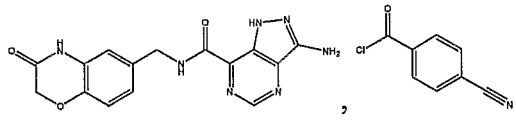
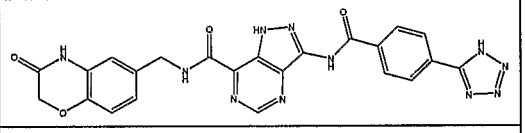
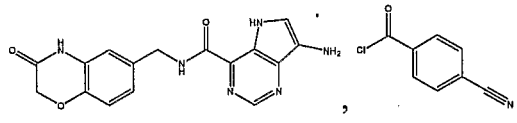
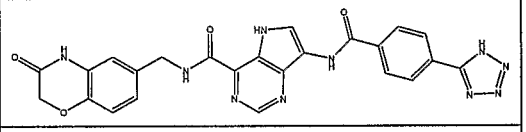
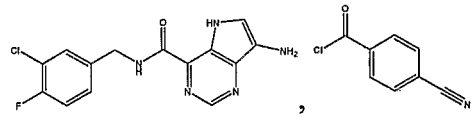
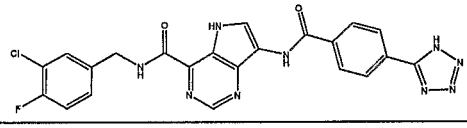
Ex. #	amine, acid chloride	product
1683		
1684		
1685		
1686		
1687		
1688		
1689		

Examples 1690-1699

[0617] If one were to follow a similar procedure as described in Example 299, except using the acid chlorides indicated in Table II-38 below and if one were to treat the obtained nitriles similarly as described in Example 469, the following compounds would be obtained.

Table II-38

Ex. #	amine, acid chloride	product
1690		
1691		

Ex. #	amine, acid chloride	product
1692		
1693		
1694		
1695		
1696		
1697		
1698		
1699		

Example 1700

Assay for Determining MMP-13 Inhibition

[0618] The typical assay for MMP-13 activity is carried out in assay buffer comprised of 50 mM Tris, pH 7.5, 150 mM NaCl, 5 mM $CaCl_2$ and 0.05% Brij-35. Different concentrations of tested compounds are prepared in assay buffer in 50 μL aliquots. 10 μL of a 50 nM stock solution of catalytic domain of MMP-13 enzyme (produced by Alantos) is added to the compound solution. The mixture of enzyme and compound in assay buffer is thoroughly mixed and incubated for 10 min at room temperature. Upon the completion of incubation, the assay is started by addition of 40 μL of a 12.5 μM stock solution of MMP-13 fluorescent substrate (Calbiochem, Cat. No. 444235). The time-dependent increase in

fluorescence is measured at the 320 nm excitation and 390 nm emission by automatic plate multireader. The IC_{50} values are calculated from the initial reaction rates.

Example 1701

Assay for Determining MMP-3 Inhibition

[0619] The typical assay for MMP-3 activity is carried out in assay buffer comprised of 50 mM MES, pH 6.0, 10 mM $CaCl_2$ and 0.05% Brij-35. Different concentrations of tested compounds are prepared in assay buffer in 50 μL aliquots. 10 μL of a 100 nM stock solution of the catalytic domain of MMP-3 enzyme (Biomol, Cat. No. SE-109) is added to the compound solution. The mixture of enzyme and compound in assay buffer is thoroughly mixed and incubated for 10 min at room temperature. Upon the completion of incubation, the assay is started by addition of 40 μL of a 12.5 μM stock solution of NFF-3 fluorescent substrate (Calbiochem, Cat. No. 480455). The time-dependent increase in fluorescence is measured at the 330 nm excitation and 390 nm emission by automatic plate multireader. The IC_{50} values are calculated from the initial reaction rates

Example 1702

Assay for Determining MMP-8 Inhibition

[0620] The typical assay for MMP-8 activity is carried out in assay buffer comprised of 50 mM Tris, pH 7.5, 150 mM NaCl, 5 mM $CaCl_2$ and 0.05% Brij-35. Different concentrations of tested compounds are prepared in assay buffer in 50 μL aliquots. 10 μL of a 50 nM stock solution of activated MMP-8 enzyme (Calbiochem, Cat. No. 444229) is added to the compound solution. The mixture of enzyme and compound in assay buffer is thoroughly mixed and incubated for 10 min at room temperature. Upon the completion of incubation, the assay is started by addition of 40 μL of a 10 μM stock solution of OmniMMP fluorescent substrate (Biomol, Cat. No. P-126). The time-dependent increase in fluorescence is measured at the 320 nm excitation and 390 nm emission by automatic plate multireader at 37°C. The IC_{50} values are calculated from the initial reaction rates.

Example 1703

Assay for Determining MMP-12 Inhibition

[0621] The typical assay for MMP-12 activity is carried out in assay buffer comprised of 50 mM Tris, pH 7.5, 150 mM NaCl, 5 mM $CaCl_2$ and 0.05% Brij-35. Different concentrations of tested compounds are prepared in assay buffer in 50 μL aliquots. 10 μL of a 50 nM stock solution of the catalytic domain of MMP-12 enzyme (Biomol, Cat. No. SE-138) is added to the compound solution. The mixture of enzyme and compound in assay buffer is thoroughly mixed and incubated for 10 min at room temperature. Upon the completion of incubation, the assay is started by addition of 40 μL of a 12.5 μM stock solution of OmniMMP fluorescent substrate (Biomol, Cat. No. P-126). The time-dependent increase in fluorescence is measured at the 320 nm excitation and 390 nm emission by automatic plate multireader at 37°C. The IC_{50} values are calculated from the initial reaction rates.

Example 1704

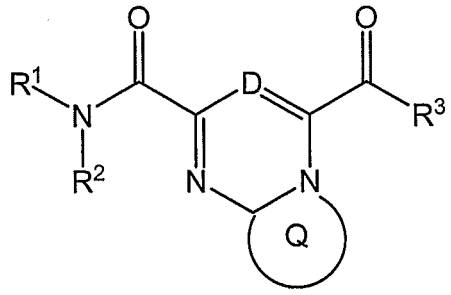
Assay for Determining Aggrecanase-1 Inhibition

[0622] The typical assay for aggrecanase-1 activity is carried out in assay buffer comprised of 50 mM Tris, pH 7.5, 150 mM NaCl, 5 mM $CaCl_2$ and 0.05% Brij-35. Different concentrations of tested compounds are prepared in assay buffer in 50 μL aliquots. 10 μL of a 75 nM stock solution of aggrecanase-1 (Invitek) is added to the compound solution. The mixture of enzyme and compound in assay buffer is thoroughly mixed. The reaction is started by addition of 40 μL of a 250 nM stock solution of aggrecan-IGD substrate (Invitek) and incubation at 37°C for exact 15 min. The reaction is stopped by addition of EDTA and the samples are analysed by using aggrecanase ELISA (Invitek, InviLISA, Cat. No. 30510111) according to the protocol of the supplier. Shortly: 100 μL of each proteolytic reaction are incubated in a pre-coated micro plate for 90 min at room temperature. After 3 times washing, antibody-peroxidase conjugate is added for 90 min at room temperature. After 5 times washing, the plate is incubated with TMB solution for 3 min at room temperature. The peroxidase reaction is stopped with sulfurous acid and the absorbance is red at 450 nm. The

IC_{50} values are calculated from the absorbance signal corresponding to residual aggrecanase activity.

WHAT IS CLAIMED IS:

1. A compound having Formula (I):



Formula (I)

wherein:

R^1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^3 is $NR^{20}R^{21}$;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-C(O)-NR^{11}-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted one or more times, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{20} is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times;

R^{21} is a bicyclic or tricyclic fused ring system, wherein at least one ring is partially saturated, and wherein the bicyclic or tricyclic fused ring system is optionally substituted one or more times;

R^{22} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N{=}CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, SO_2R^{10} , $SO_2NR^{10}R^{11}$ and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{30} is selected from the group consisting of alkyl and $(C_0\text{-}C_6)$-alkyl-aryl, wherein alkyl and aryl are optionally substituted;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted one or more times;

Q is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

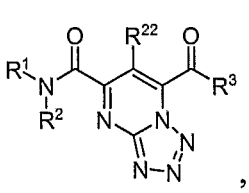
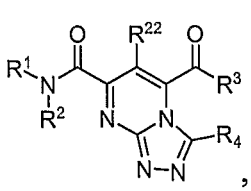
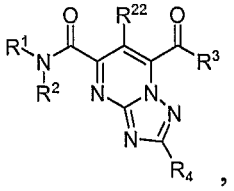
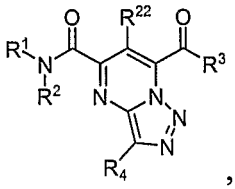
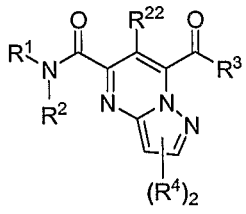
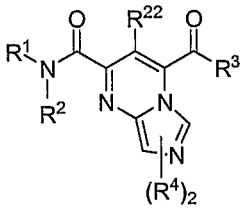
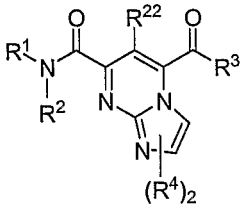
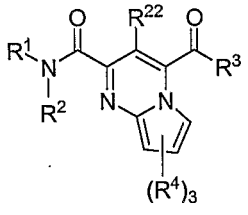
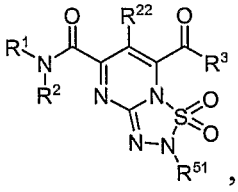
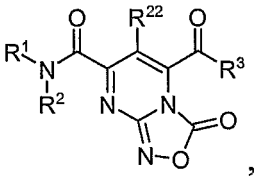
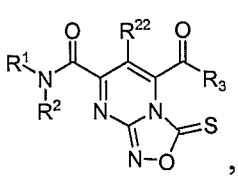
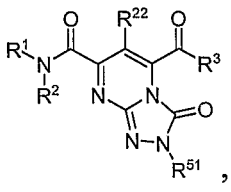
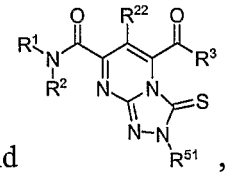
D is a member selected from the group consisting of CR^{22} and N;

x is selected from 0 to 2;

y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

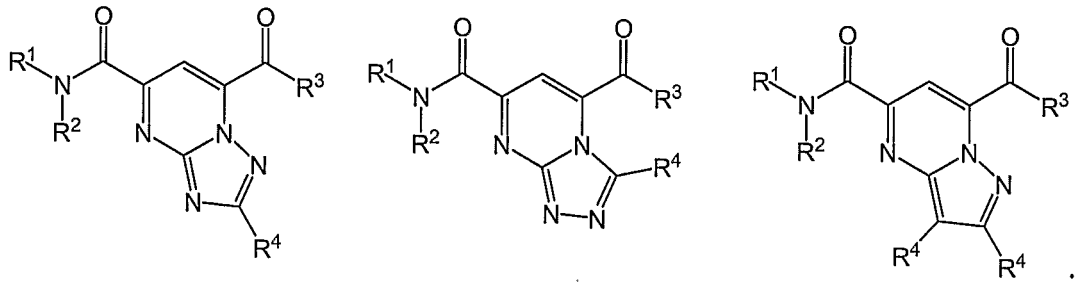
2. The compound of claim 1, selected from the group consisting of:


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and ,

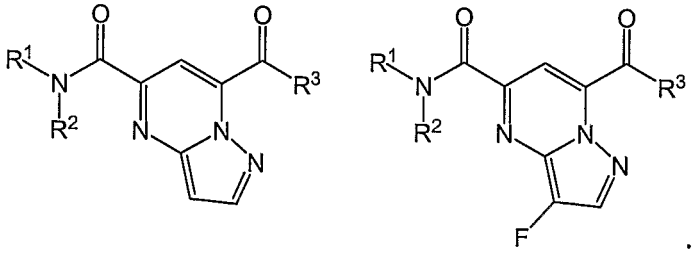
wherein:

R^{51} is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and haloalkyl, wherein alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and haloalkyl are optionally substituted one or more times.

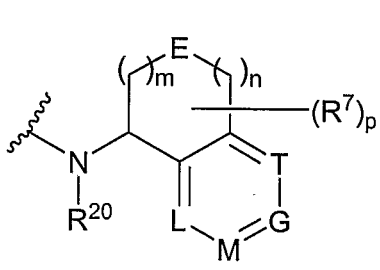
3. The compound of claim 2, selected from the group consisting of:



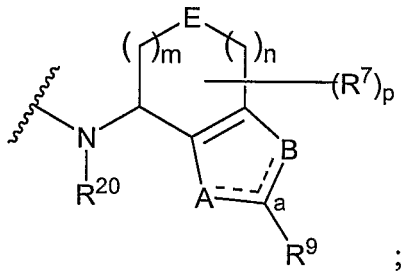
4. The compound of claim 2, selected from the group consisting of:



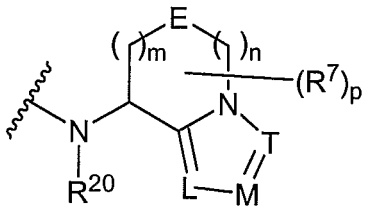
5. The compound of claim 2, wherein R^3 is selected from the group consisting of:



;



; and



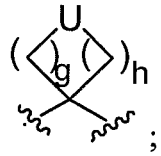
wherein:

R^5 is independently selected from the group consisting of hydrogen, alkyl, $C(O)NR^{10}R^{11}$, aryl, arylalkyl, $SO_2NR^{10}R^{11}$ and $C(O)OR^{10}$ wherein alkyl, aryl and arylalkyl are optionally substituted one or more times;

R^7 is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, halo, R^4 and $NR^{10}R^{11}$, wherein alkyl and cycloalkyl are optionally substituted one or more times, or optionally two R^7 groups together at the same carbon atom form =O, =S or $=NR^{10}$;

R^9 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, CHF_2, CF_3, OR^{10}, $COOR^{10}$, $CH(CH_3)CO_2H$, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$P(O)_2OH$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=N\text{-}CN)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=N\text{-}CN)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=N\text{-}NO_2)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=N\text{-}NO_2)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2NR^{10}$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2NR^{10}$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $S(O)_2NR^{10}$-alkyl, $S(O)_2$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $(C_0\text{-}C_6)$-alkyl-C(O)-NR^{11}-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{11}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

E is selected from the group consisting of a bond, $CR^{10}R^{11}$, O, NR^5, S, S=O, $S(=O)_2$, C(=O), $N(R^{10})(C=O)$, $(C=O)N(R^{10})$, $N(R^{10})S(=O)_2$, $S(=O)_2N(R^{10})$, C=N-OR^{11}, $-C(R^{10}R^{11})C(R^{10}R^{11})-$, $-CH_2$-W^1- and



;

W^1 is selected from the group consisting of O, NR^5, S, S=O, $S(=O)_2$, $N(R^{10})(C=O)$, $N(R^{10})S(=O)_2$ and $S(=O)_2N(R^{10})$;

U is selected from the group consisting of $C(R^5R^{10})$, NR^5, O, S, S=O and $S(=O)_2$;

A and B are independently selected from the group consisting of CR^9, CR^9R^{10}, NR^{10}, N, O and S;

G, L, M and T are independently selected from the group consisting of CR^9 and N;

g and h are independently selected from 0-2;

m and n are independently selected from 0-3, provided that:

(1) when E is present, m and n are not both 3;

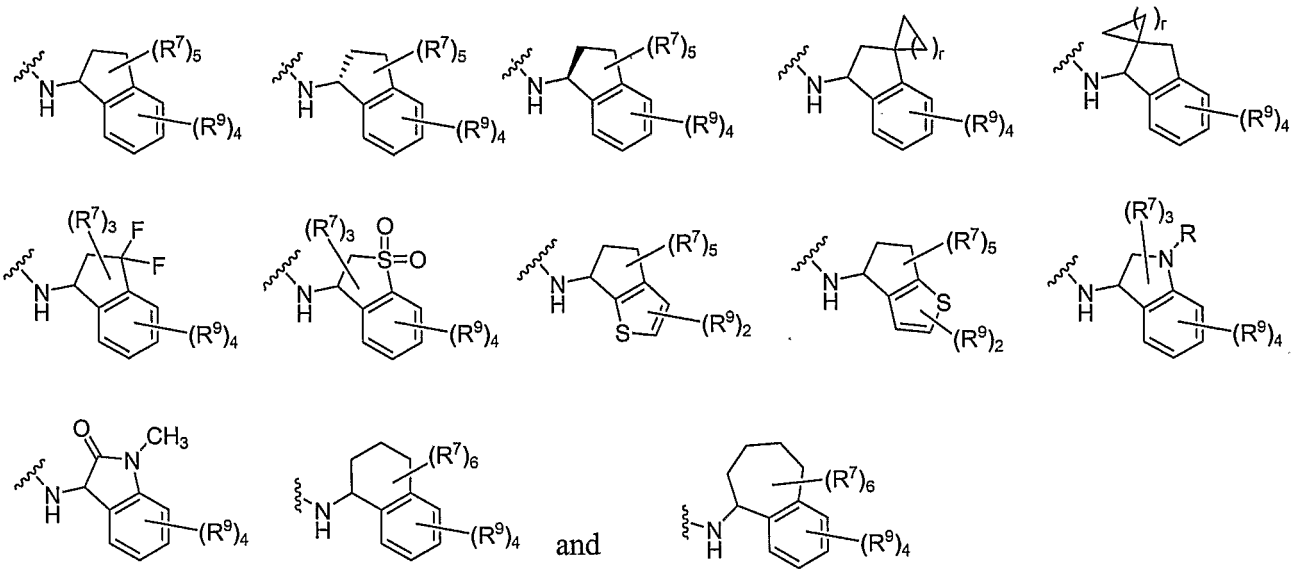
(2) when E is $-CH_2-W^1-$, m and n are not 3; and

(3) when E is a bond, m and n are not 0; and

p is selected from 0-6;

wherein the dotted line represents a double bond between one of: carbon "a" and A, or carbon "a" and B.

6. The compound according to claim 5, wherein R^3 is selected from the group consisting of:

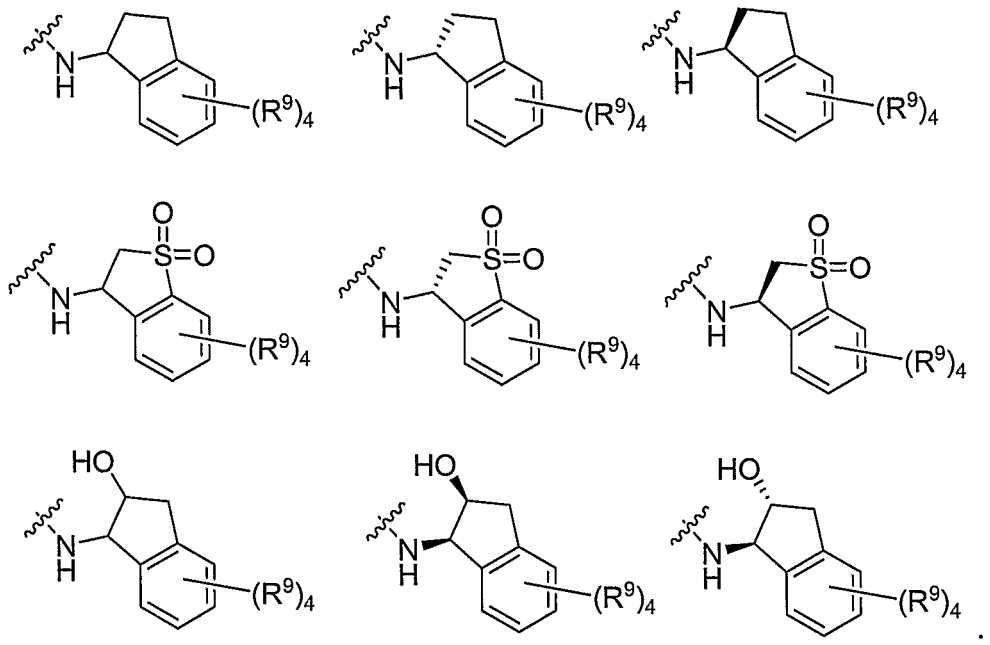


wherein:

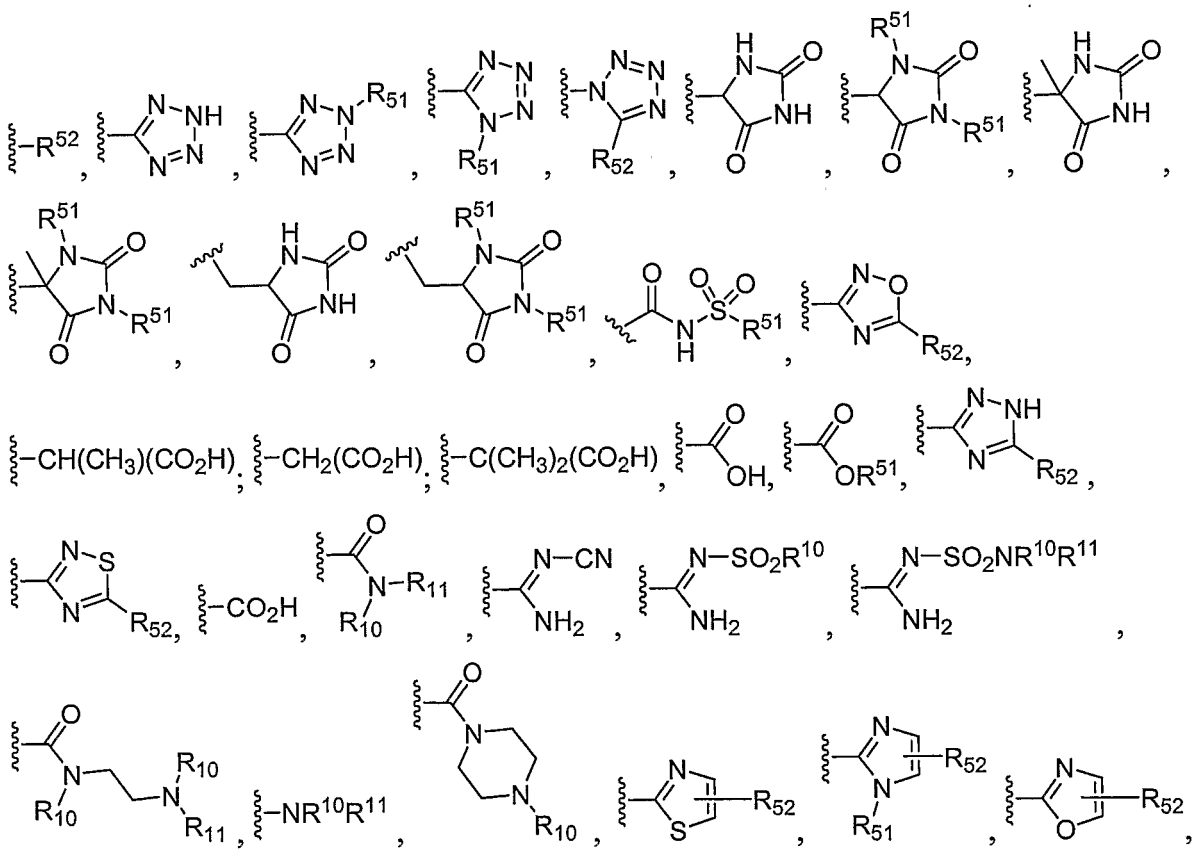
R is selected from the group consisting of $C(O)NR^{10}R^{11}$, COR^{10}, $SO_2NR^{10}R^{11}$, SO_2R^{10}, $CONHCH_3$ and $CON(CH_3)_2$, wherein $C(O)NR^{10}R^{11}$, COR^{10}, $SO_2NR^{10}R^{11}$, SO_2R^{10}, $CONHCH_3$ and $CON(CH_3)_2$ are optionally substituted one or more times; and

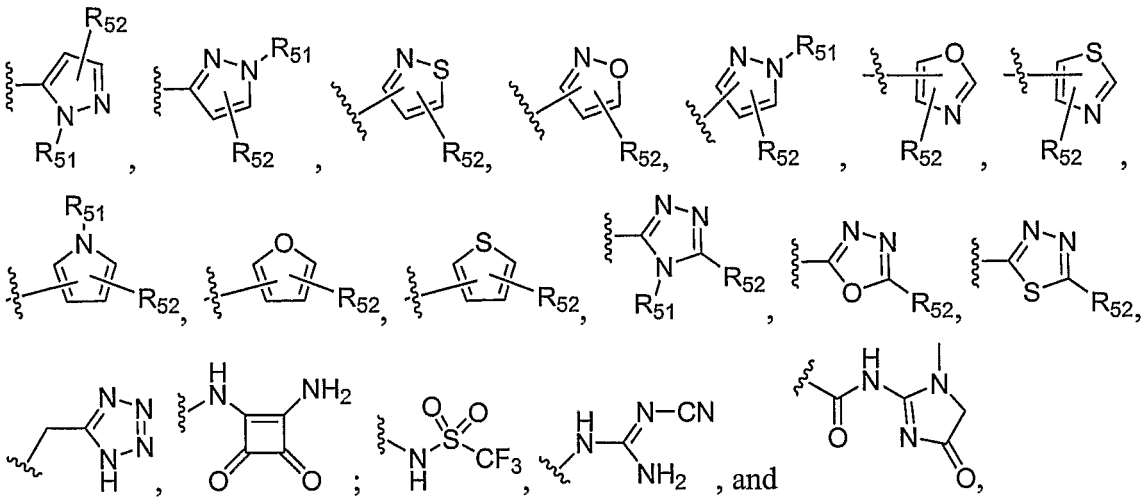
r is selected from 1-4.

7. The compound according to claim 5, wherein R^3 is selected from the group consisting of:



8. The compound according to claim 7, wherein R^9 is selected from the group consisting of:

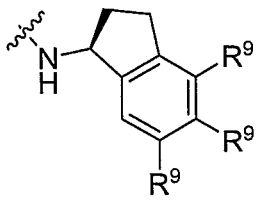




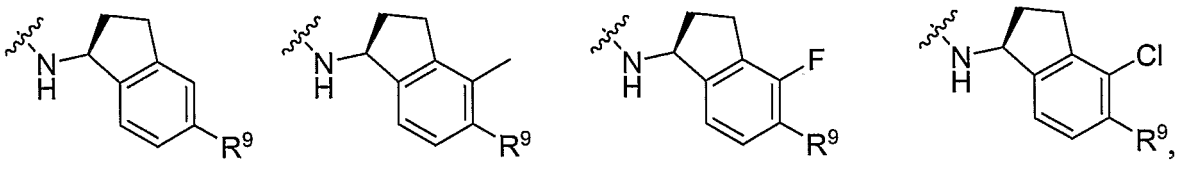
wherein:

R^{52} is selected from the group consisting of hydrogen, halo, CN, hydroxy, alkoxy, fluoroalkoxy, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, haloalkyl, $C(O)NR^{10}R^{11}$ and $SO_2NR^{10}R^{11}$, wherein alkoxy, fluoroalkoxy, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, and haloalkyl are optionally substituted one or more times.

9. The compound according to claim 5, wherein R^3 is

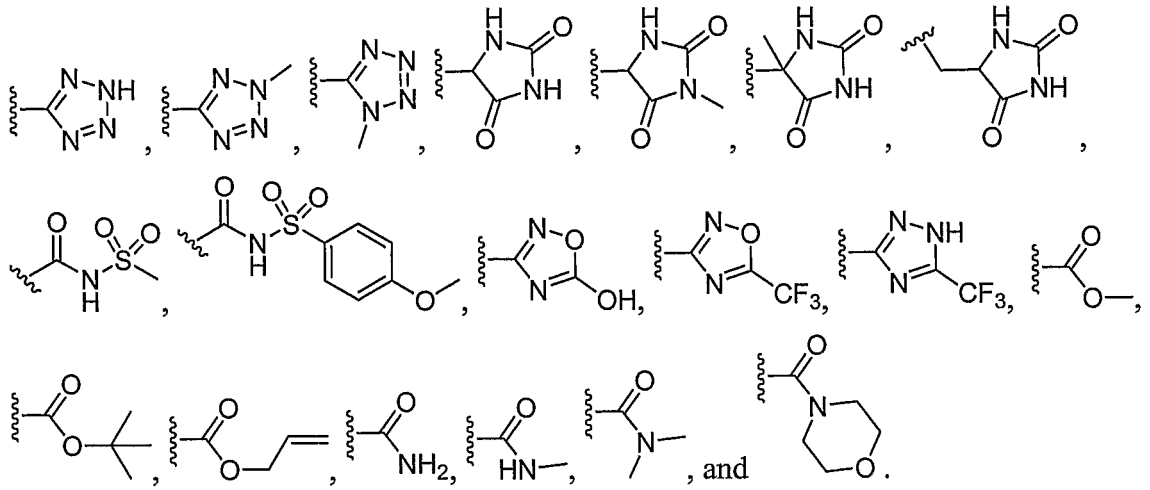


10. The compound according to claim 9, wherein R^3 is selected from the group consisting of:

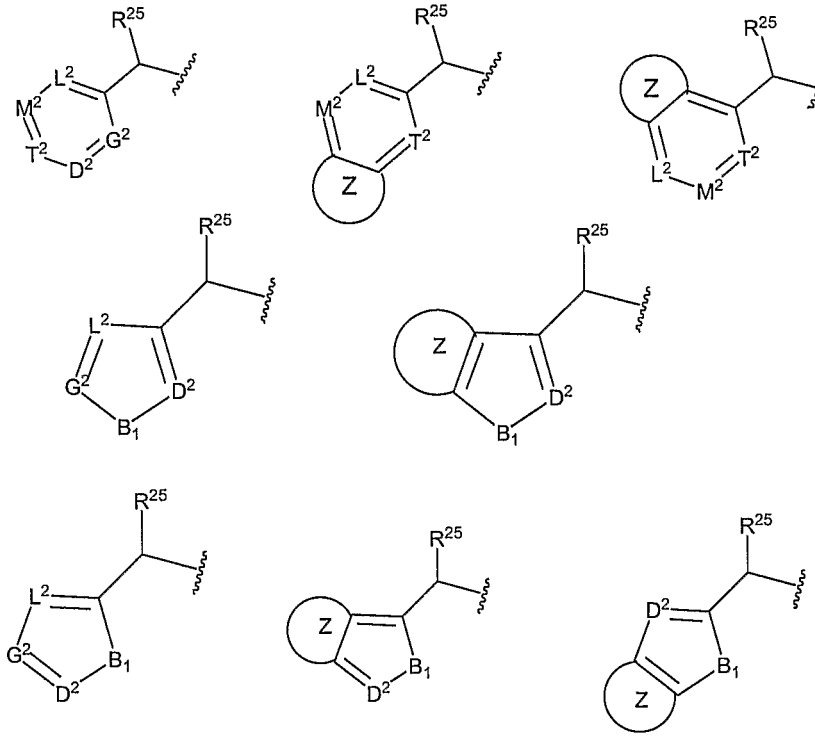


wherein:

R^9 is selected from the group consisting of hydrogen, fluoro, halo, CN, alkyl, CO_2H,



11. The compound according to claim 2, wherein R^1 is selected from the group consisting of:



wherein:

R^{18} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl are optionally substituted one or more times;

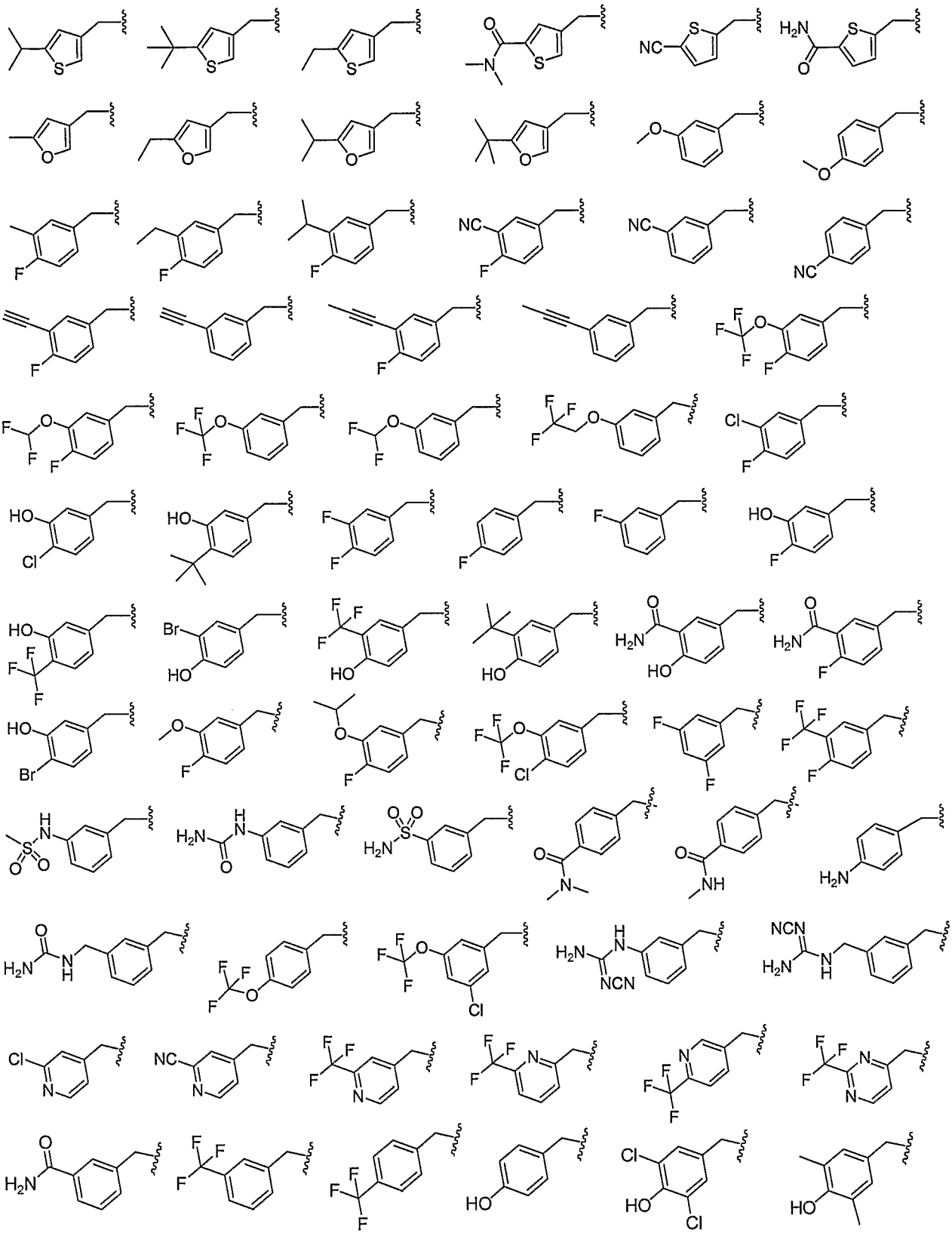
R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $C(O)NR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

B_1 is selected from the group consisting of NR^{10}, O and S;

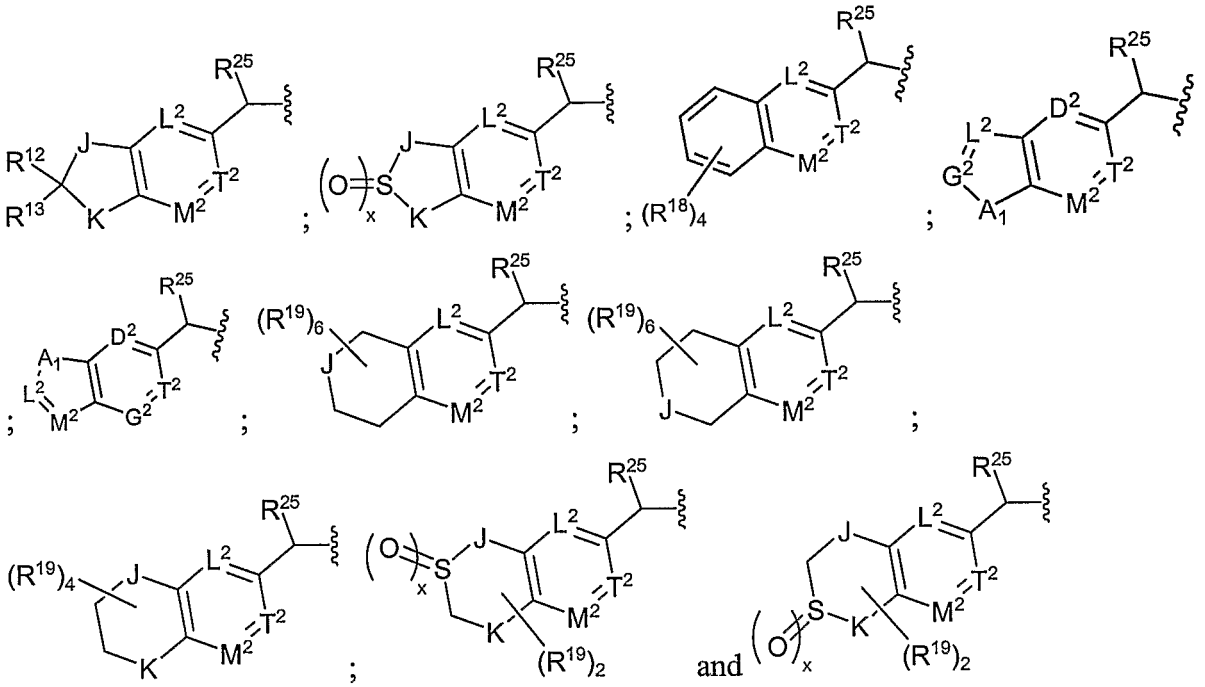
D^2, G^2, L^2, M^2 and T^2 are independently selected from the group consisting of CR^{18} and N; and

Z is a 5- to 8-membered ring selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted one or more times.

12. The compound according to claim 11, wherein R^1 is selected from the group consisting of:



13. The compound of claim 2, wherein R^1 is selected from the group consisting of:



wherein:

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, alkyl and halo, wherein alkyl is optionally substituted one or more times, or optionally R^{12} and R^{13} together form =O, =S or $=NR^{10}$;

R^{18} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{19} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two R^{19} groups together at one carbon atom form =O, =S or $=NR^{10}$;

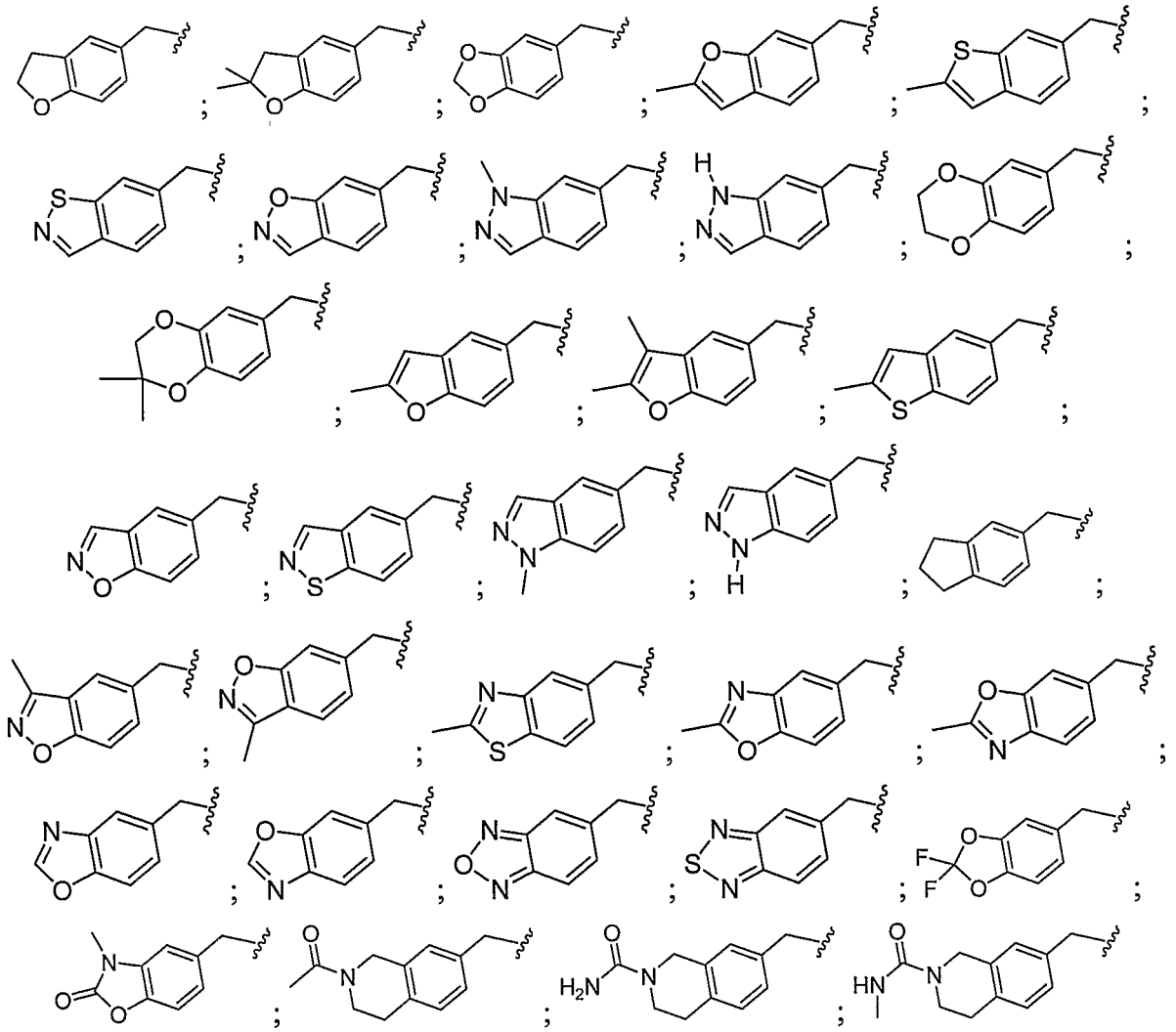
R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $C(O)NR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

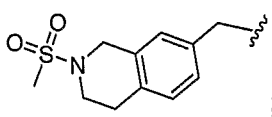
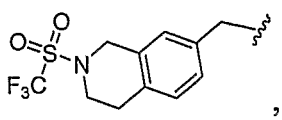
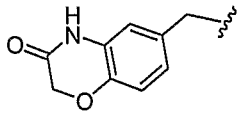
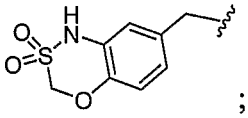
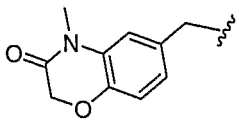
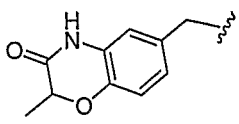
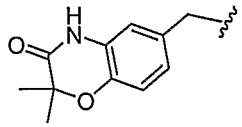
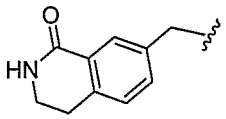
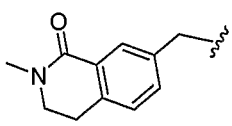
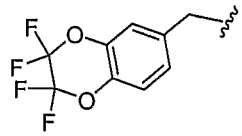
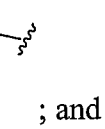
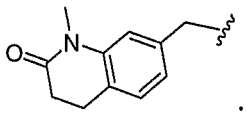
J and K are independently selected from the group consisting of $CR^{10}R^{18}$, NR^{10}, O and $S(O)_x$;

A_1 is selected from the group consisting of NR^{10}, O and S; and

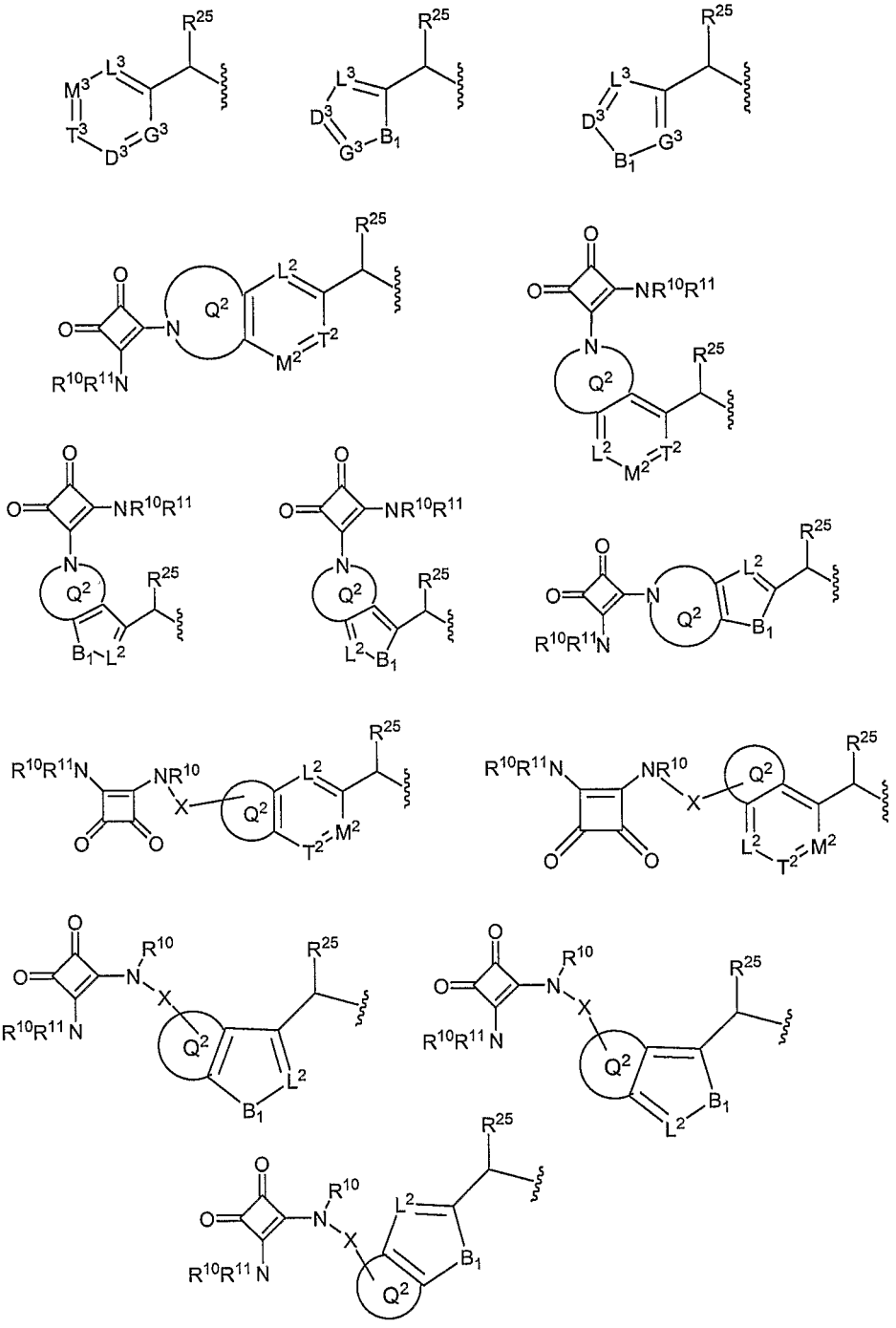
D^2, G^2, L^2, M^2 and T^2 are independently selected from the group consisting of CR^{18} and N.

14. The compound of claim 13, wherein R^1 is selected from the group consisting of:




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;

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;

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;

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; and

.

15. The compound of claim 2, wherein R^1 is selected from the group consisting of:



wherein:

R^5 is independently selected from the group consisting of hydrogen, alkyl, $C(O)NR^{10}R^{11}$, aryl, arylalkyl, $SO_2NR^{10}R^{11}$ and $C(O)OR^{10}$ wherein alkyl, aryl and arylalkyl are optionally substituted one or more times;

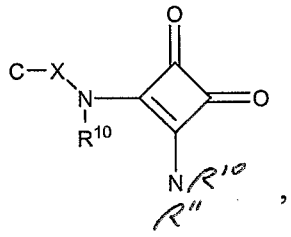
R^{18} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{19} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two R^{19} groups together at one carbon atom form =O, =S or $=NR^{10}$;

R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $CONR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl and haloalkyl are optionally substituted one or more times;

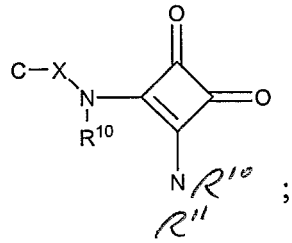
L^2, M^2, and T^2 are independently selected from the group consisting of CR^{18} and N;

D^3, G^3, L^3, M^3, and T^3 are independently selected from N, CR^{18}, and



,

with the provision that one of L^3, M^3, T^3, D^3, and G^3 is

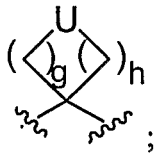


;

B_1 is selected from the group consisting of NR^{10}, O and S;

X is selected from the group consisting of a bond and $(CR^{10}R^{11})_wE(CR^{10}R^{11})_w$

E is selected from the group consisting of a bond, $CR^{10}R^{11}$, O, NR^5, S, S=O, $S(=O)_2$, $C(=O)$, $N(R^{10})(C=O)$, $(C=O)N(R^{10})$, $N(R^{10})S(=O)_2$, $S(=O)_2N(R^{10})$, $C=N\text{-}OR^{11}$, $-C(R^{10}R^{11})C(R^{10}R^{11})-$, $-CH_2\text{-}W^1-$ and



;

W^1 is selected from the group consisting of O, NR^5, S, S=O, $S(=O)_2$, $N(R^{10})(C=O)$, $N(R^{10})S(=O)_2$ and $S(=O)_2N(R^{10})$;

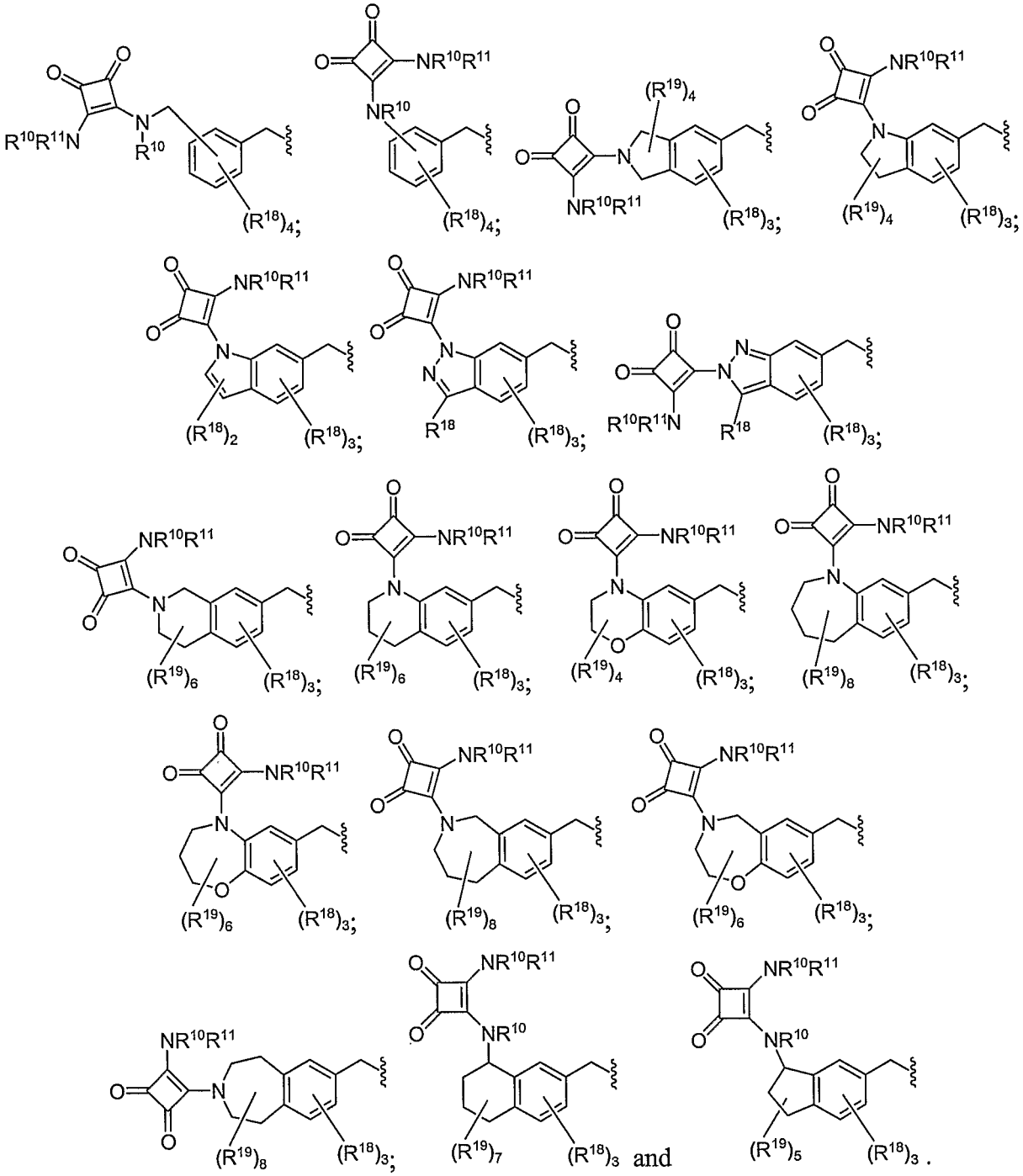
U is selected from $C(R^5R^{10})$, NR^5, O, S, S=O, $S(=O)_2$;

g and h are independently selected from 0-2;

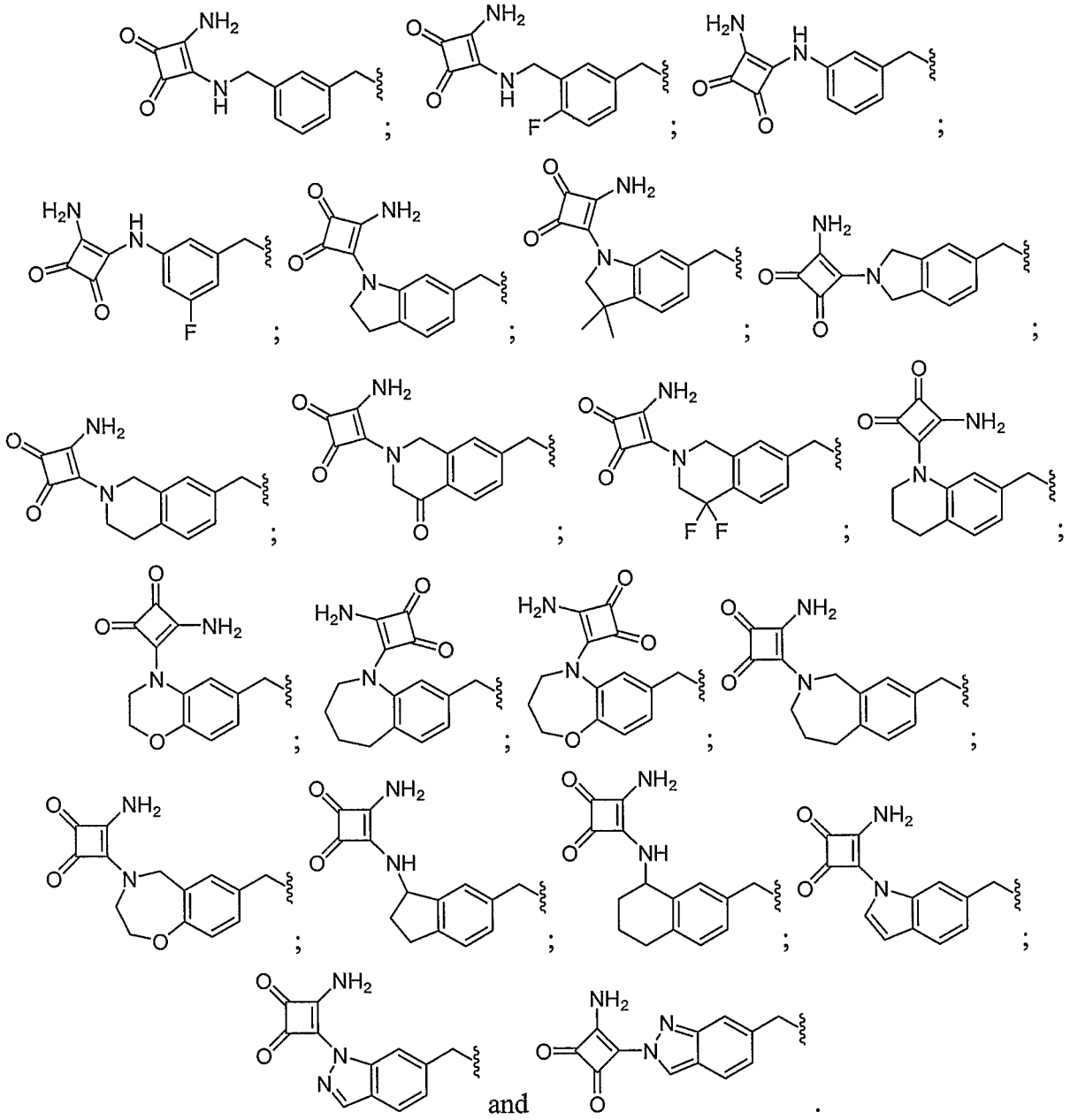
w is selected from 0-4; and

Q^2 is a 5- to 8-membered ring consisting of cycloalkyl, heterocycloalkyl, aryl, heteroaryl, which is optionally substituted one or more times with R^{19}.

16. The compound of claim 15, wherein R^1 is selected from the group consisting of:

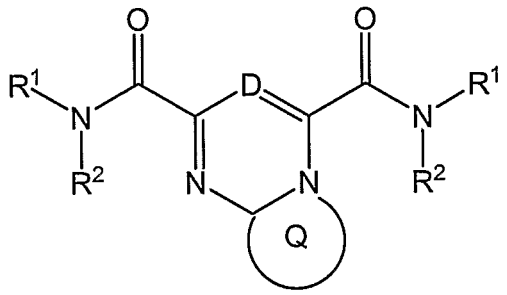


17. The compound of claim 15, wherein R^1 is selected from the group consisting of:



and .

18. A compound having Formula (II):



Formula (II)

wherein:

R^1 in each occurrence is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0$-$C_6)$-

alkyl-COR^{10}, (C_0-C_6)-alkyl-OR^{10}, (C_0-C_6)-alkyl-$NR^{10}R^{11}$, (C_0-C_6)-alkyl-NO_2, (C_0-C_6)-alkyl-CN, (C_0-C_6)-alkyl-$S(O)_yOR^{10}$, (C_0-C_6)-alkyl-$S(O)_yNR^{10}R^{11}$, (C_0-C_6)-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, ($C_0$-$C_6$)-alkyl-$S(O)_xR^{10}$, ($C_0$-$C_6$)-alkyl-$OC(O)R^{10}$, ($C_0$-$C_6$)-alkyl-$OC(O)NR^{10}R^{11}$, ($C_0$-$C_6$)-alkyl-$C(=NR^{10})NR^{10}R^{11}$, ($C_0$-$C_6$)-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, ($C_0$-$C_6$)-alkyl-$C(O)OR^{10}$, ($C_0$-$C_6$)-alkyl-$C(O)NR^{10}R^{11}$, ($C_0$-$C_6$)-alkyl-$C(O)NR^{10}SO_2R^{11}$, ($C_0$-$C_6$)-alkyl-C(O)-$NR^{11}$-CN, O-($C_0$-$C_6$)-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-(C_0-C_6)-alkyl-$C(O)OR^{10}$, $S(O)_x$-(C_0-C_6)-alkyl-$C(O)NR^{10}R^{11}$, (C_0-C_6)-alkyl-$C(O)NR^{10}$-(C_0-C_6)-alkyl-$NR^{10}R^{11}$, (C_0-C_6)-alkyl-NR^{10}-$C(O)R^{10}$, (C_0-C_6)-alkyl-NR^{10}-$C(O)OR^{10}$, (C_0-C_6)-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, (C_0-C_6)-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, (C_0-C_6)-alkyl-NR^{10}-$S(O)_yR^{10}$, O-(C_0-C_6)-alkyl-aryl and O-(C_0-C_6)-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{22} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N=CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, SO_2R^{10} , $SO_2NR^{10}R^{11}$ and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted one or more times;

Q is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

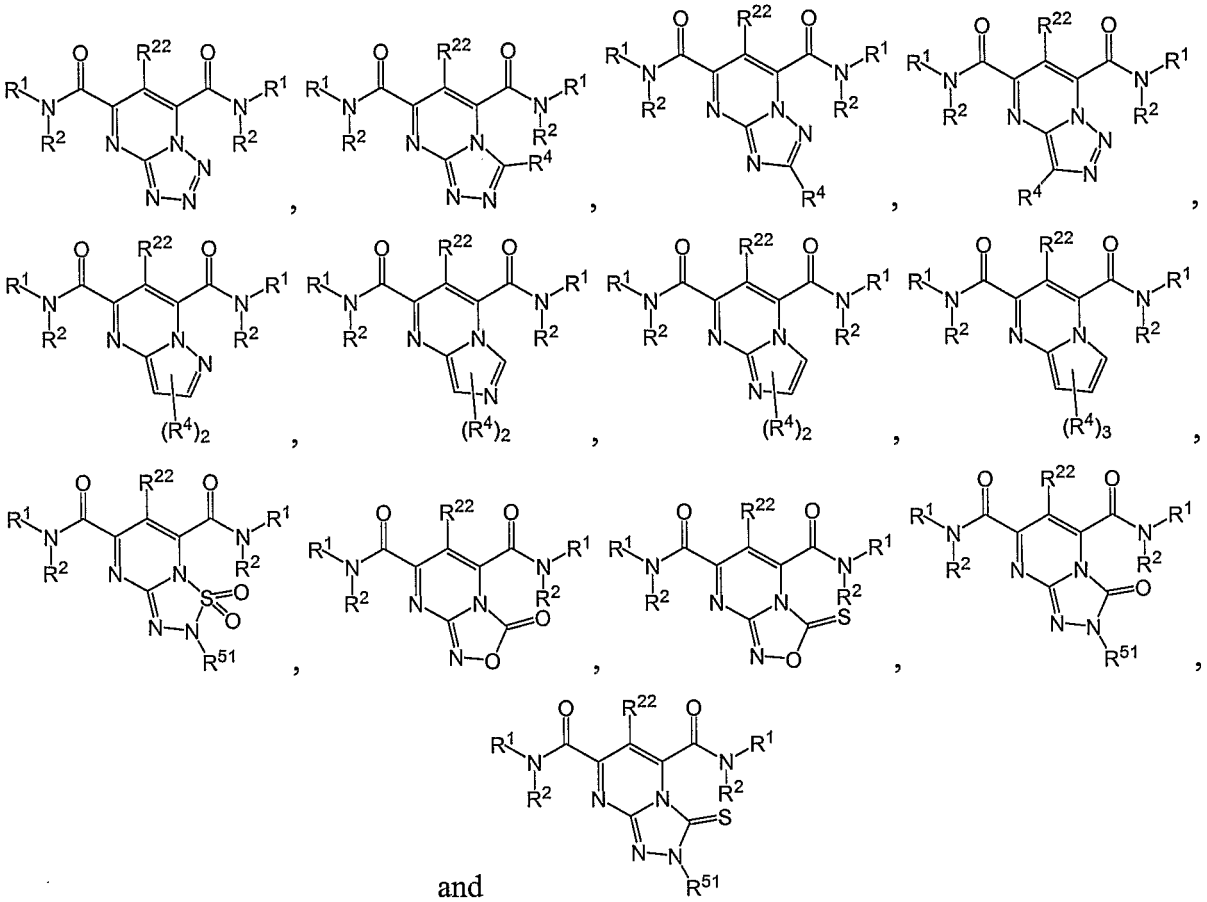
D is a member selected from the group consisting of CR^{22} and N;

x is selected from 0 to 2;

y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

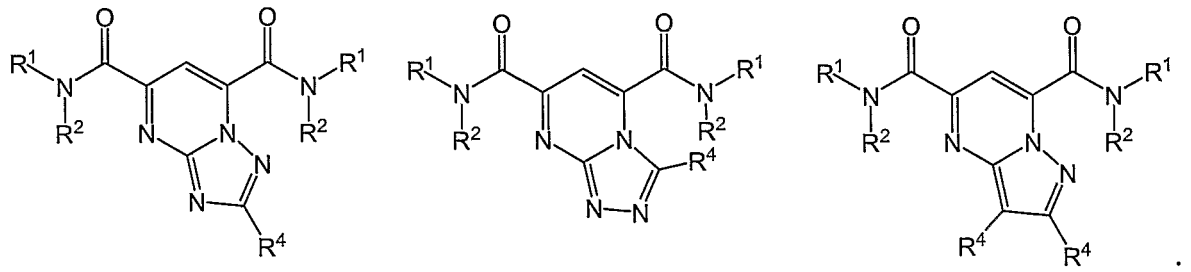
19. The compound of claim 18, selected from the group consisting of:



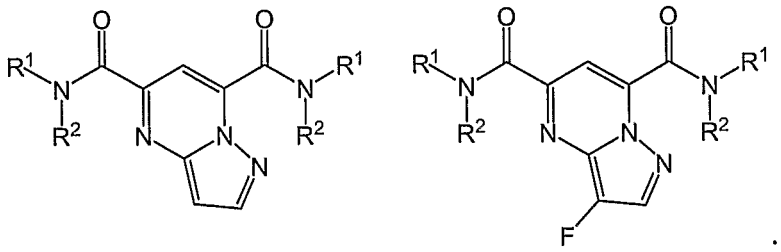
wherein:

R^{51} is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and haloalkyl, wherein alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and haloalkyl are optionally substituted one or more times.

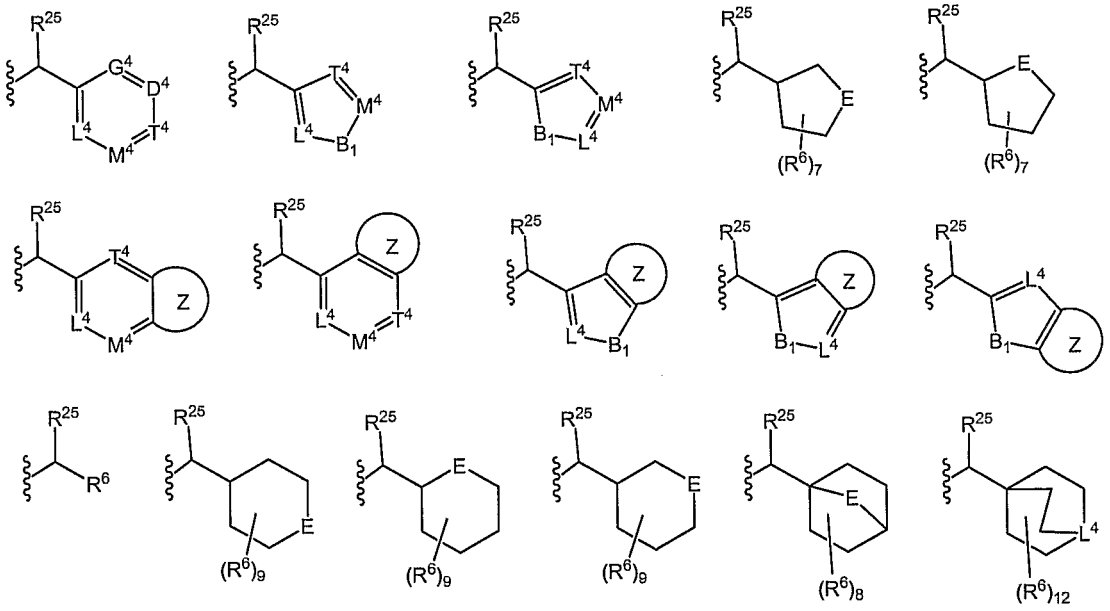
20. The compound of claim 19, selected from the group consisting of:



21. The compound of claim 20, selected from the group consisting of:



22. The compound of claim 19, wherein at least one R^1 is selected from the group consisting of:



wherein:

R^5 is independently selected from the group consisting of hydrogen, alkyl, $C(O)NR^{10}R^{11}$, aryl, arylalkyl, $SO_2NR^{10}R^{11}$ and $C(O)OR^{10}$ wherein alkyl, aryl and arylalkyl are optionally substituted one or more times;

R^6 is selected from the group consisting of R^9, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $C(O)OR^{10}$, $CH(CH_3)CO_2H$, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-

alkyl-$P(O)_2OH$, (C_0-C_6)-alkyl-$S(O)_yNR^{10}R^{11}$, (C_0-C_6)-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, (C_0-C_6)-alkyl-$S(O)_xR^{10}$, (C_0-C_6)-alkyl-$OC(O)R^{10}$, (C_0-C_6)-alkyl-$OC(O)NR^{10}R^{11}$, (C_0-C_6)-alkyl-$C(=NR^{10})NR^{10}R^{11}$, (C_0-C_6)-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, (C_0-C_6)-alkyl-$NR^{10}C(=N-CN)NR^{10}R^{11}$, (C_0-C_6)-alkyl-$C(=N-CN)NR^{10}R^{11}$, (C_0-C_6)-alkyl-$NR^{10}C(=N-NO_2)NR^{10}R^{11}$, (C_0-C_6)-alkyl-$C(=N-NO_2)NR^{10}R^{11}$, (C_0-C_6)-alkyl-$C(O)OR^{10}$, (C_0-C_6)-alkyl-$C(O)NR^{10}R^{11}$, (C_0-C_6)-alkyl-$C(O)NR^{10}SO_2R^{11}$, $C(O)NR^{10}$-(C_0-C_6)-alkyl-heteroaryl, $C(O)NR^{10}$-(C_0-C_6)-alkyl-aryl, $S(O)_2NR^{10}$-(C_0-C_6)-alkyl-aryl, $S(O)_2NR^{10}$-(C_0-C_6)-alkyl-heteroaryl, $S(O)_2NR^{10}$-alkyl, $S(O)_2$-(C_0-C_6)-alkyl-aryl, $S(O)_2$-(C_0-C_6)-alkyl-heteroaryl, (C_0-C_6)-alkyl-$C(O)$-NR^{11}-CN, O-(C_0-C_6)-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-(C_0-C_6)-alkyl-$C(O)OR^{10}$, $S(O)_x$-(C_0-C_6)-alkyl-$C(O)NR^{10}R^{11}$, (C_0-C_6)-alkyl-$C(O)NR^{10}$-(C_0-C_6)-alkyl-$NR^{10}R^{11}$, (C_0-C_6)-alkyl-NR^{10}-$C(O)R^{10}$, (C_0-C_6)-alkyl-NR^{10}-$C(O)OR^{10}$, (C_0-C_6)-alkyl-NR^{10}-$C(O)$-$NR^{10}R^{11}$, (C_0-C_6)-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, (C_0-C_6)-alkyl-NR^{10}-$S(O)_yR^{11}$, O-(C_0-C_6)-alkyl-aryl and O-(C_0-C_6)-alkyl-heteroaryl, wherein each R^6 group is optionally substituted by one or more R^{14} groups;

R^9 is independently selected from the group consisting of hydrogen, alkyl, halo, CHF_2, CF_3, OR^{10}, $NR^{10}R^{11}$, NO_2, and CN, wherein alkyl is optionally substituted one or more times;

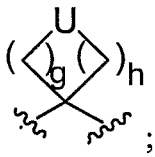
R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $C(O)NR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

R^{30} is selected from the group consisting of alkyl and (C_0-C_6)-alkyl-aryl, wherein alkyl and aryl are optionally substituted;

B_1 is selected from the group consisting of NR^{10}, O and S;

D^4, G^4, L^4, M^4, and T^4 are independently selected from CR^6 or N;

E is selected from the group consisting of a bond, $CR^{10}R^{11}$, O, NR^5, S, S=O, $S(=O)_2$, C(=O), $N(R^{10})(C=O)$, $(C=O)N(R^{10})$, $N(R^{10})S(=O)_2$, $S(=O)_2N(R^{10})$, C=N-OR^{11}, -$C(R^{10}R^{11})C(R^{10}R^{11})$-, -$CH_2$-$W^1$- and



;

W^1 is selected from the group consisting of O, NR^5, S, S=O, $S(=O)_2$, $N(R^{10})(C=O)$, $N(R^{10})S(=O)_2$ and $S(=O)_2N(R^{10})$;

U is selected from $C(R^5R^{10})$, NR^5, O, S, S=O, $S(=O)_2$;

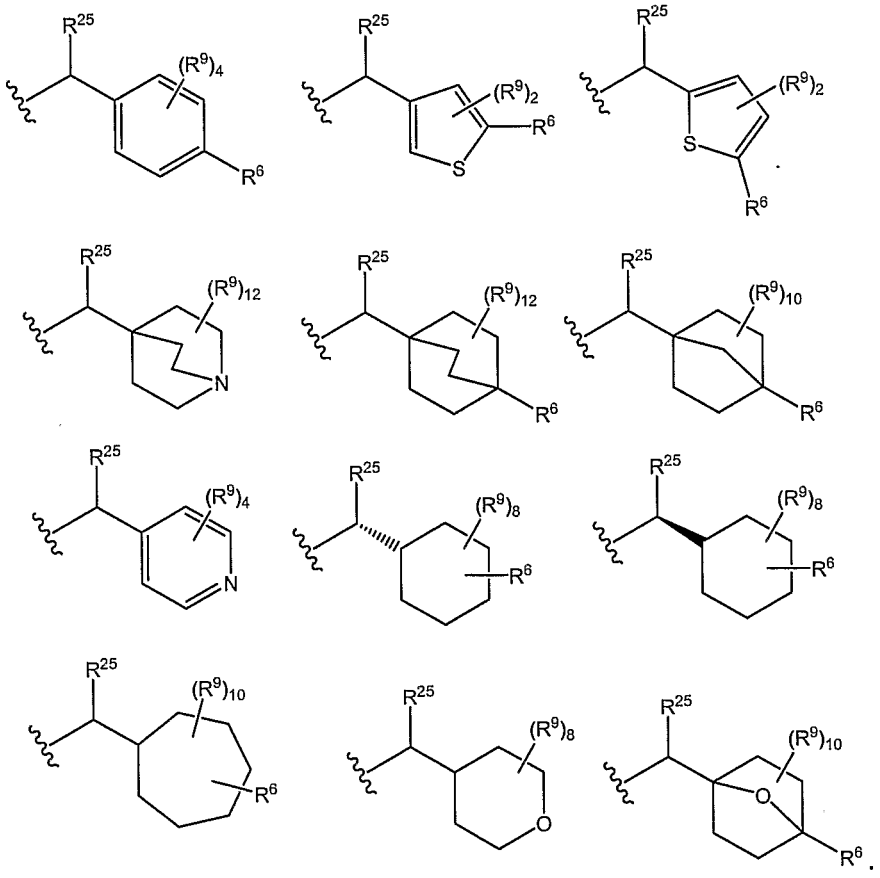
g and h are independently selected from 0-2;

x is selected from 0-2;

y is selected from 1 and 2; and

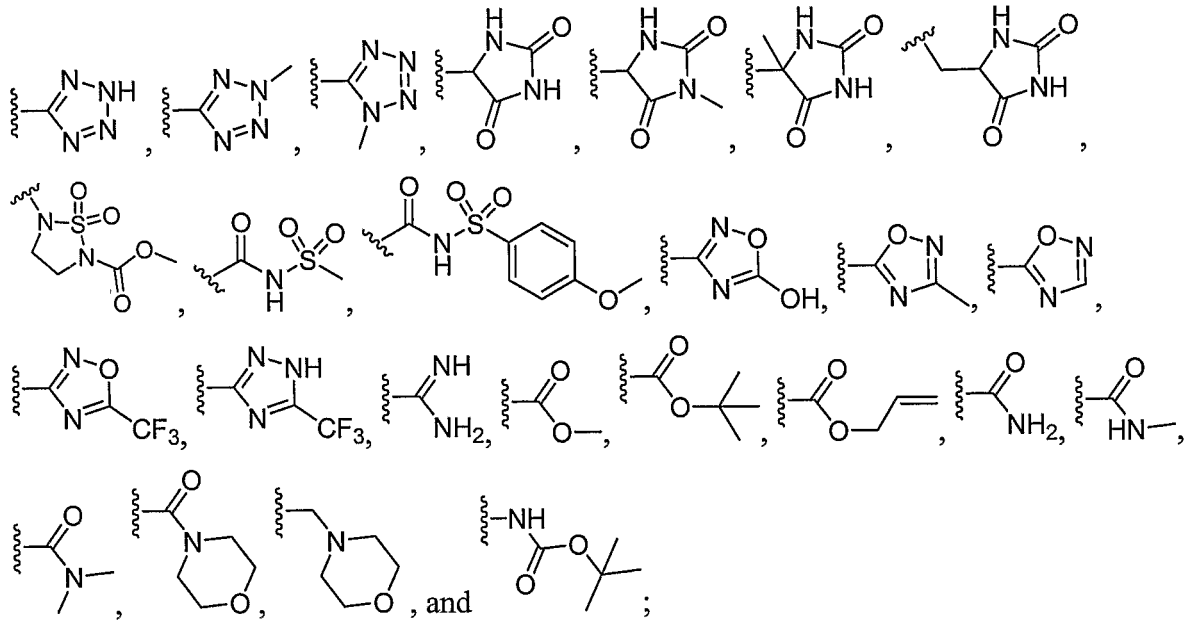
Z is a 5- to 8-membered ring consisting of cycloalkyl, heterocycloalky, aryl and heteroaryl, wherein cycloalkyl, heterocycloalky, aryl and heteroaryl are optionally substituted one ore more times.

23. The compound of claim 22, wherein at least one R^1 is selected from the group consisting of:



24. The compound of claim 23, wherein:

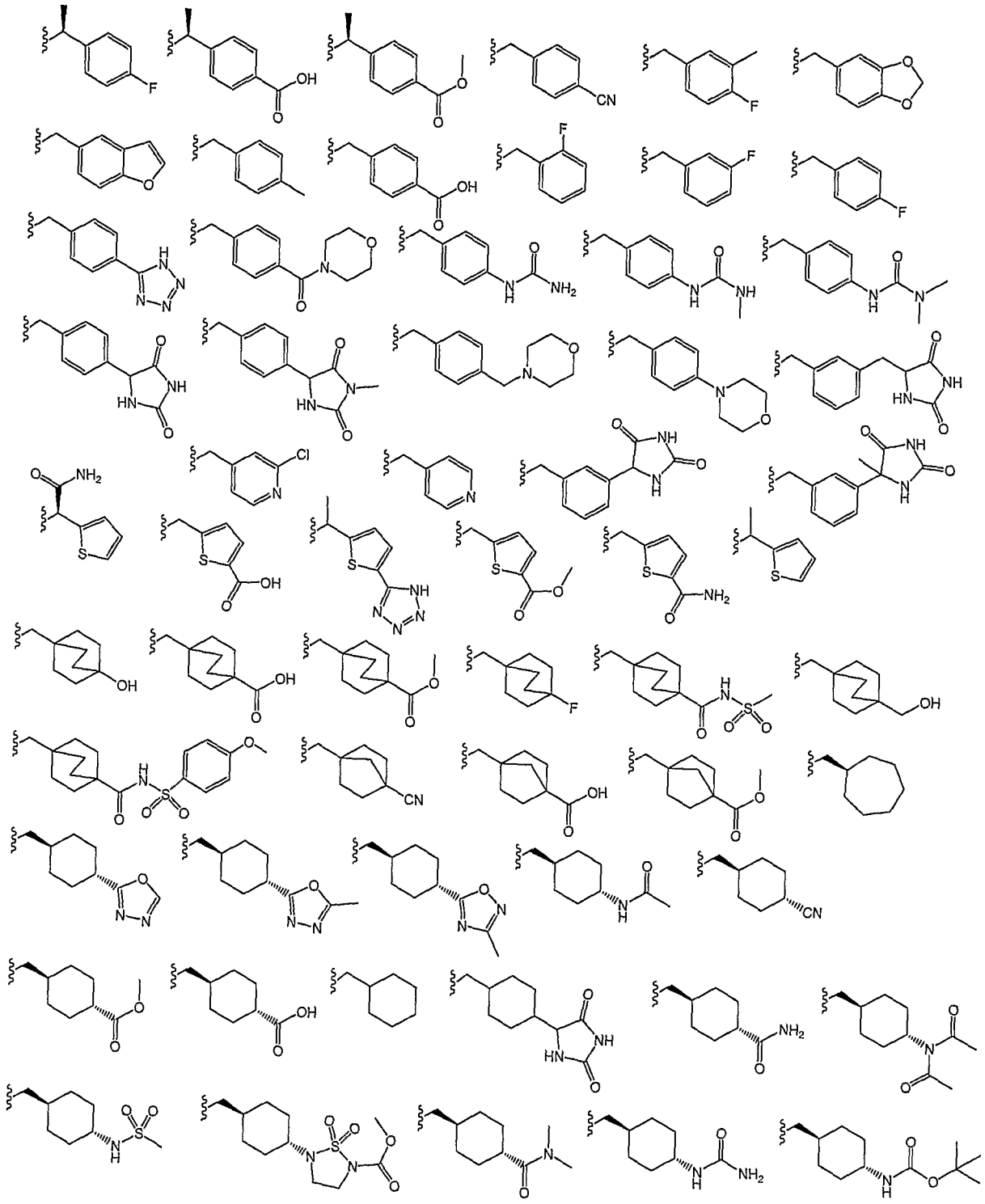
R^6 is selected from the group consisting of hydrogen, halo, CN, OH, CH_2OH, CF_3, CHF_2, OCF_3, $OCHF_2$, $COCH_3$, SO_2CH_3, SO_2CF_3, SO_2NH_2, SO_2NHCH_3, $SO_2N(CH_3)_2$, NH_2, $NHCOCH_3$, $N(COCH_3)_2$, $NHCONH_2$, $NHSO_2CH_3$, alkoxy, alkyl, CO_2H,

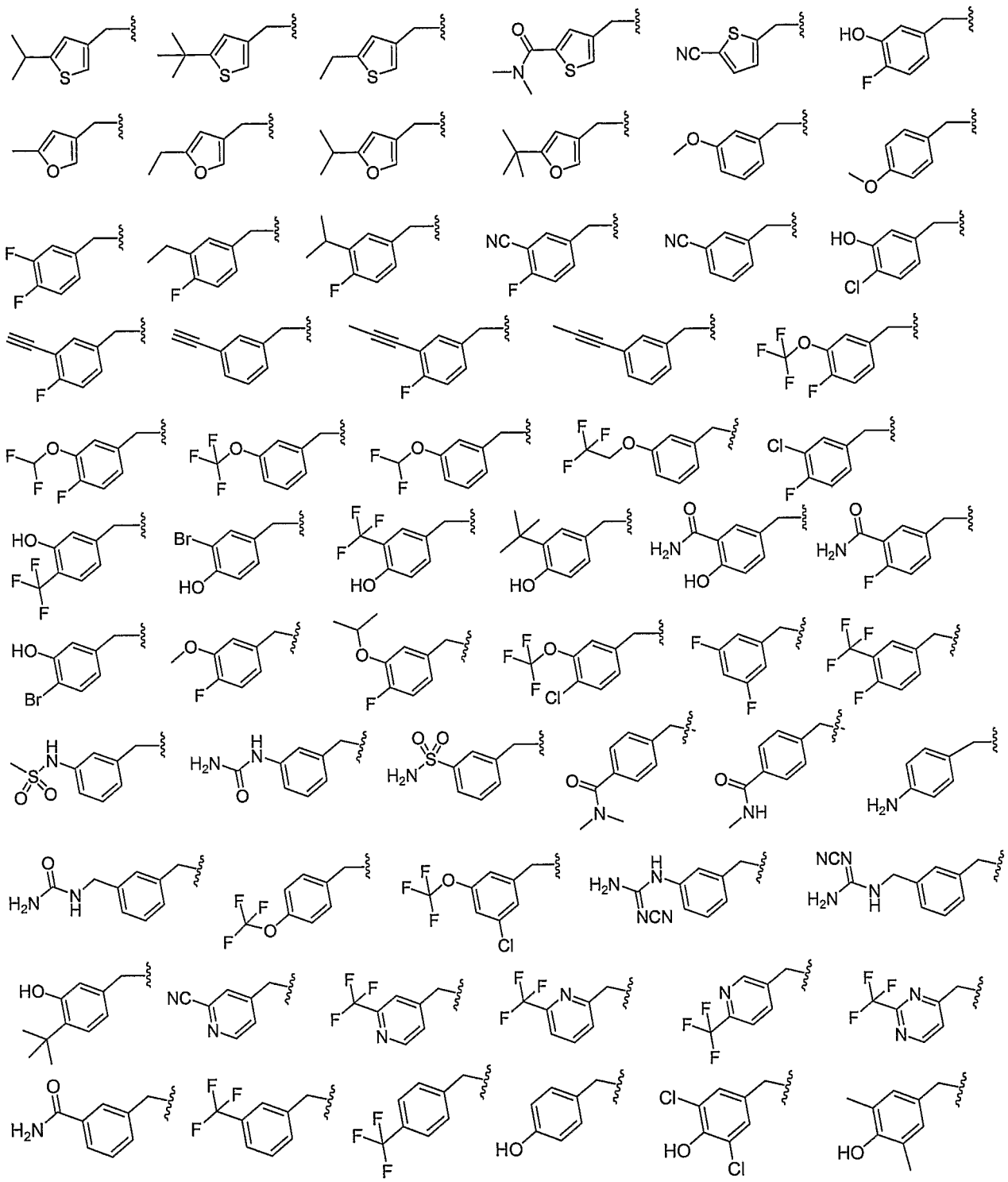


R^9 is independently selected from the group consisting of hydrogen, fluoro, chloro, CH_3, CF_3, CHF_2, OCF_3, and $OCHF_2$;

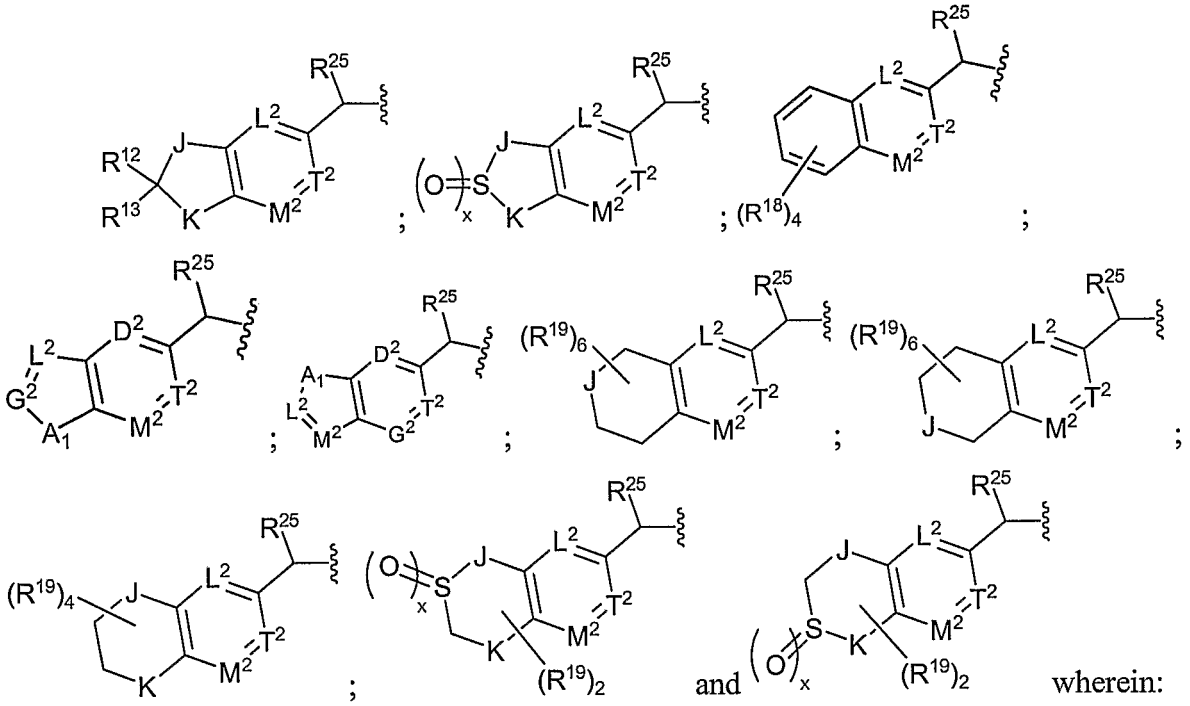
R^{25} is selected from the group consisting of hydrogen, CH_3, COOMe, COOH, and $CONH_2$.

25. The compound of claim 22, wherein at least one R^1 is selected from the group consisting of:





26. The compound of claim 19, wherein at least one R^1 is selected from the group consisting of:



wherein:

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, alkyl and halo, wherein alkyl is optionally substituted one or more times, or optionally R^{12} and R^{13} together form =O, =S or $=NR^{10}$;

R^{18} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{19} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two R^{19} groups together at one carbon atom form =O, =S or $=NR^{10}$;

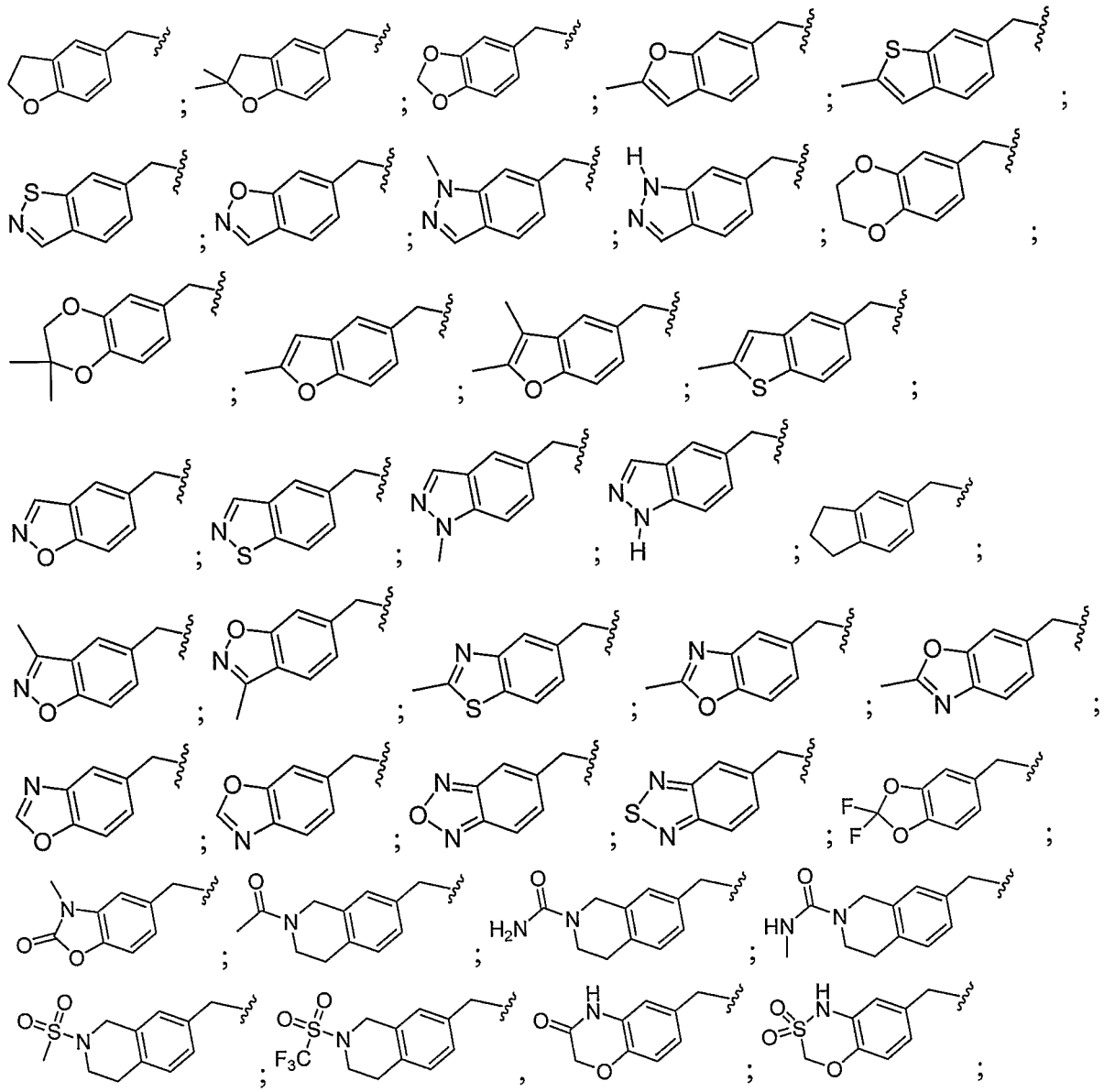
R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $C(O)NR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

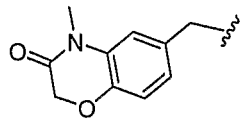
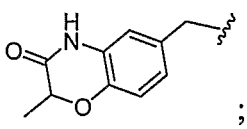
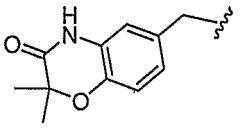
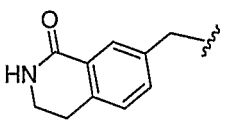
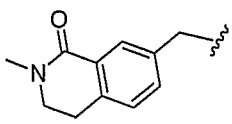
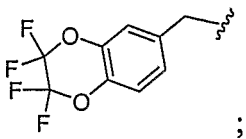
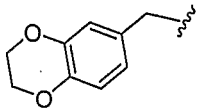
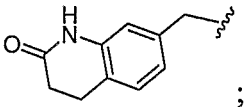
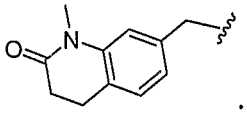
J and K are independently selected from the group consisting of $CR^{10}R^{18}$, NR^{10}, O and $S(O)_x$;

A_1 is selected from the group consisting of NR^{10}, O and S; and

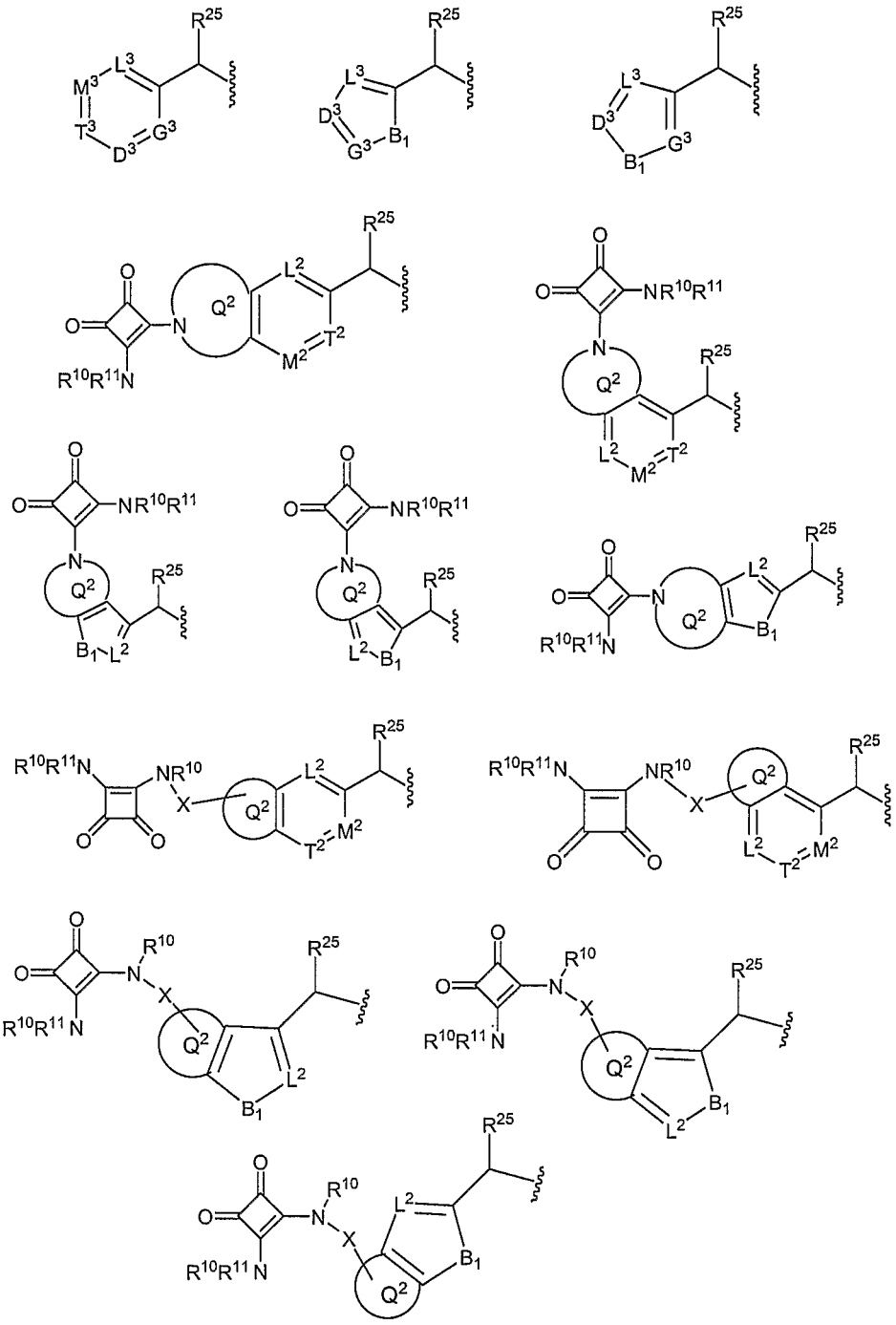
D^2, G^2, L^2, M^2 and T^2 are independently selected from the group consisting of CR^{18} and N.

27. The compound of claim 26, wherein at least one R^1 is selected from the group consisting of:




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; and

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28. The compound of claim 19, wherein one R^1 is selected from the group consisting of:



wherein:

R^5 is independently selected from the group consisting of hydrogen, alkyl, $C(O)NR^{10}R^{11}$, aryl, arylalkyl, $SO_2NR^{10}R^{11}$ and $C(O)OR^{10}$ wherein alkyl, aryl and arylalkyl are optionally substituted one or more times;

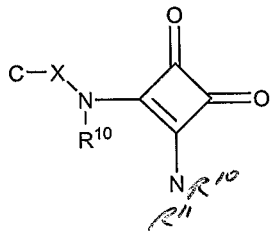
R^{18} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{19} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two R^{19} groups together at one carbon atom form =O, =S or $=NR^{10}$;

R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $CONR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl and haloalkyl are optionally substituted one or more times;

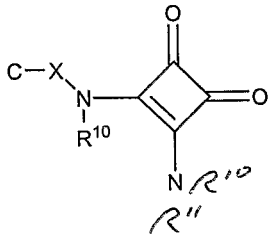
L^2, M^2, and T^2 are independently selected from the group consisting of CR^{18} and N;

L^3, M^3, T^3, D^3, and G^3 are independently selected from N, CR^{18}, and



,

with the provision that one of L^3, M^3, T^3, D^3, and G^3 is

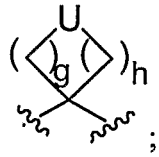


;

B_1 is selected from the group consisting of NR^{10}, O and S;

X is selected from the group consisting of a bond and $(CR^{10}R^{11})_wE(CR^{10}R^{11})_w$

E is selected from the group consisting of a bond, $CR^{10}R^{11}$, O, NR^5, S, S=O, $S(=O)_2$, C(=O), $N(R^{10})(C=O)$, $(C=O)N(R^{10})$, $N(R^{10})S(=O)_2$, $S(=O)_2N(R^{10})$, C=N-OR^{11}, $-C(R^{10}R^{11})C(R^{10}R^{11})-$, $-CH_2-W^1-$ and



;

W^1 is selected from the group consisting of O, NR^5, S, S=O, $S(=O)_2$, $N(R^{10})(C=O)$, $N(R^{10})S(=O)_2$ and $S(=O)_2N(R^{10})$;

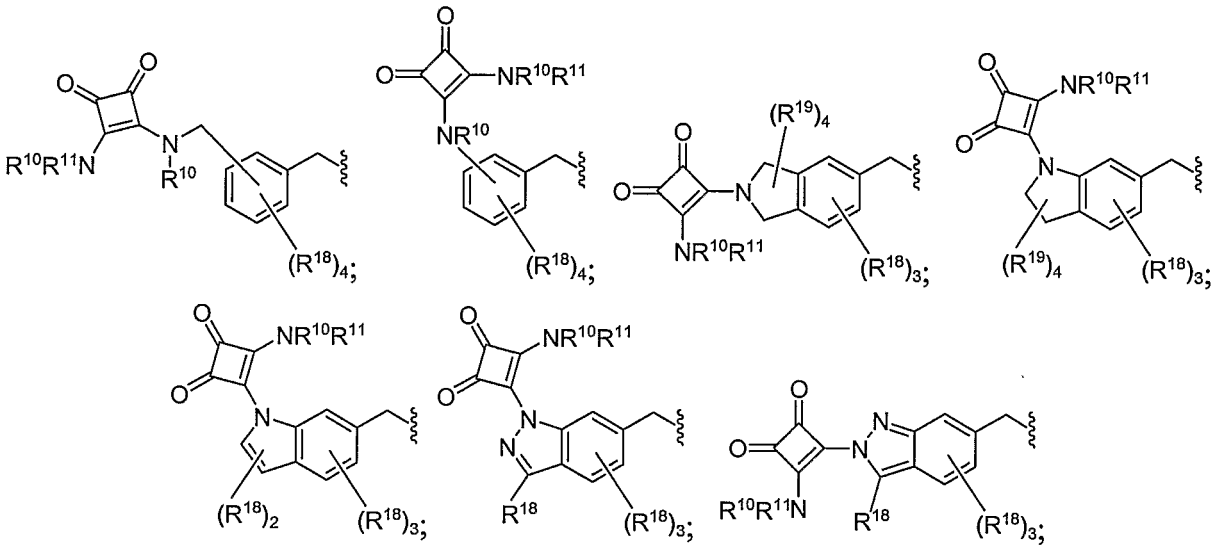
U is selected from $C(R^5R^{10})$, NR^5, O, S, S=O, $S(=O)_2$;

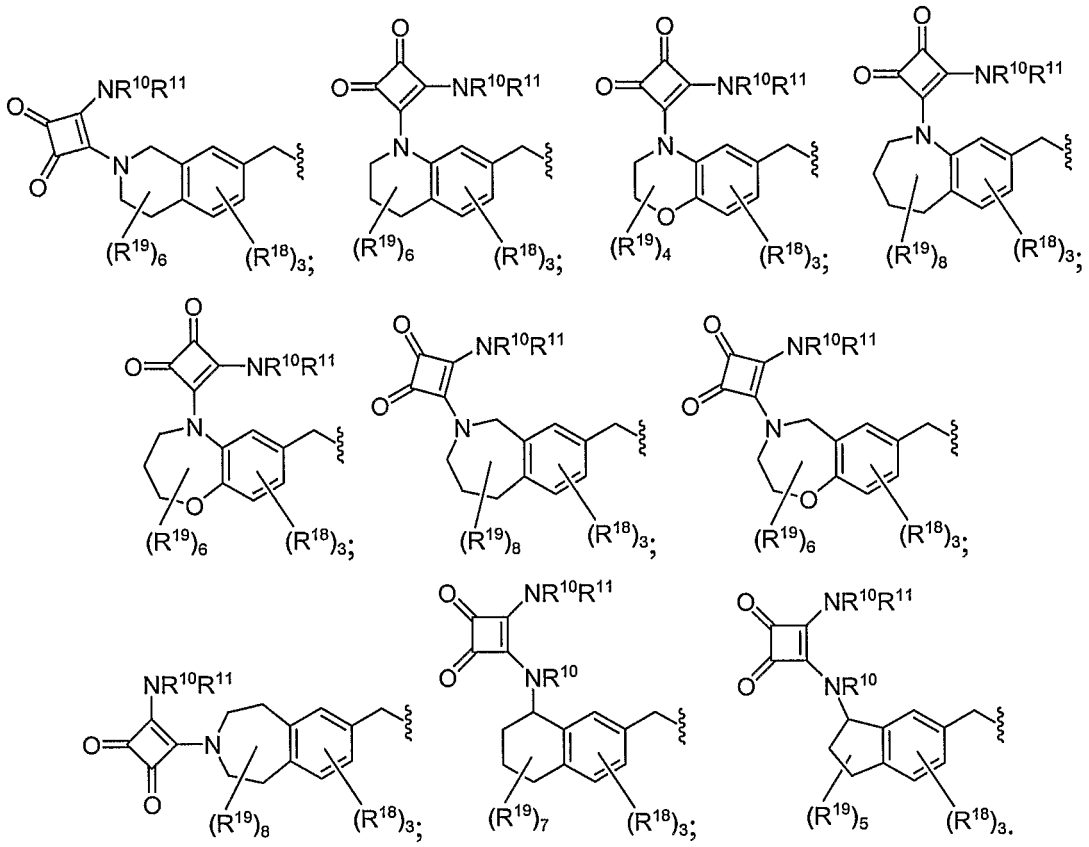
g and h are independently selected from 0-2;

w is selected from 0-4; and

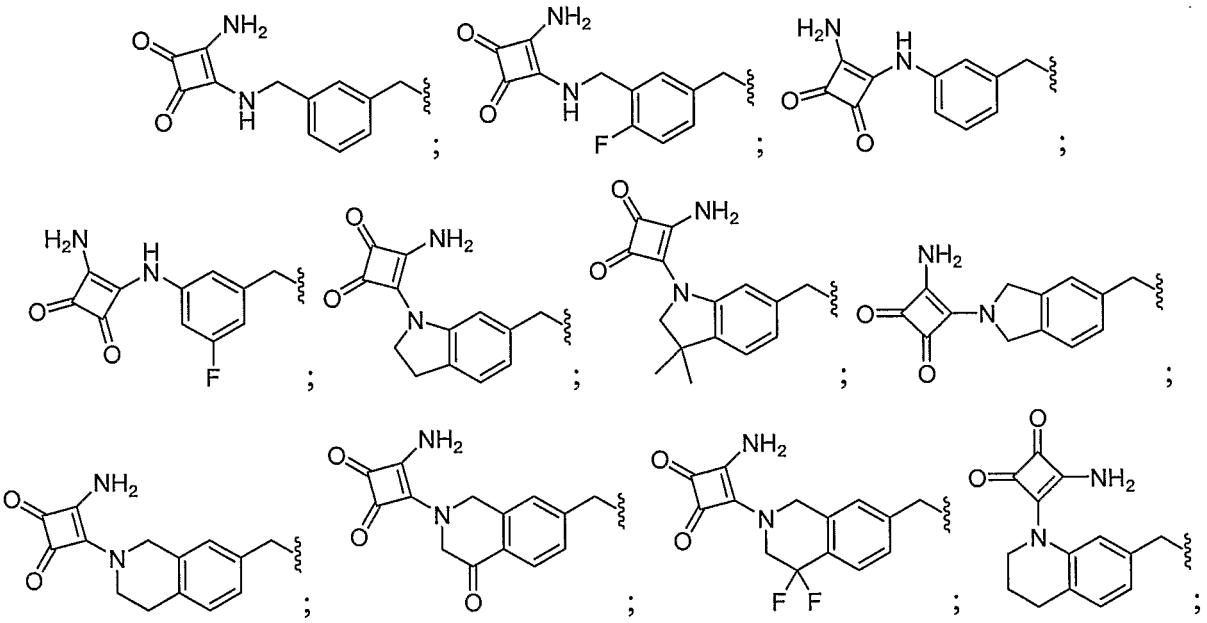
Q^2 is a 5- to 8-membered ring consisting of cycloalkyl, heterocycloalkyl, aryl, heteroaryl, which is optionally substituted one or more times with R^{19}.

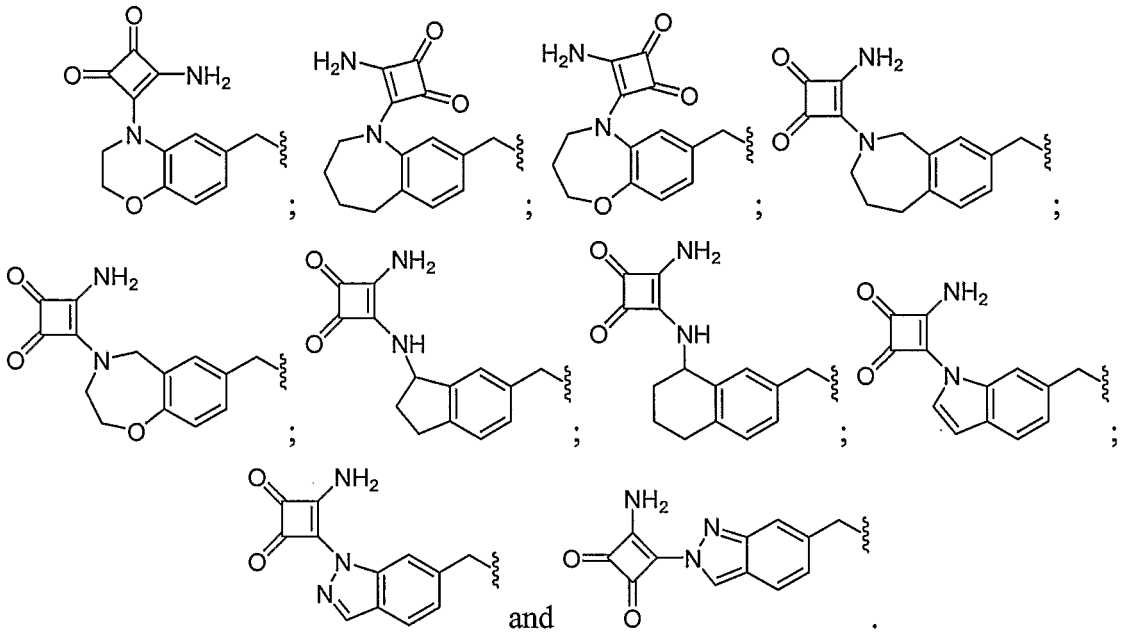
29. The compound of claim 28, wherein one R^1 is selected from the group consisting of:



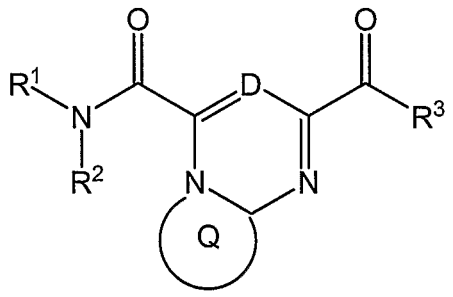


30. The compound of claim 29, wherein one R^1 is selected from the group consisting of:





31. A compound having Formula (III):



Formula (III)

wherein:

R^1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl

fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^3 is $NR^{20}R^{21}$;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)\text{-}NR^{11}$-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)\text{-}NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted one or more times, or R^{10} and R^{11} when taken together

with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{20} is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times;

R^{21} is a bicyclic or tricyclic fused ring system, wherein at least one ring is partially saturated, and wherein the bicyclic or tricyclic fused ring system is optionally substituted one or more times;

R^{22} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N{=}CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, SO_2R^{10}, $SO_2NR^{10}R^{11}$ and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{30} is selected from the group consisting of alkyl and $(C_0\text{-}C_6)$-alkyl-aryl, wherein alkyl and aryl are optionally substituted;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and

optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted one or more times;

Q is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

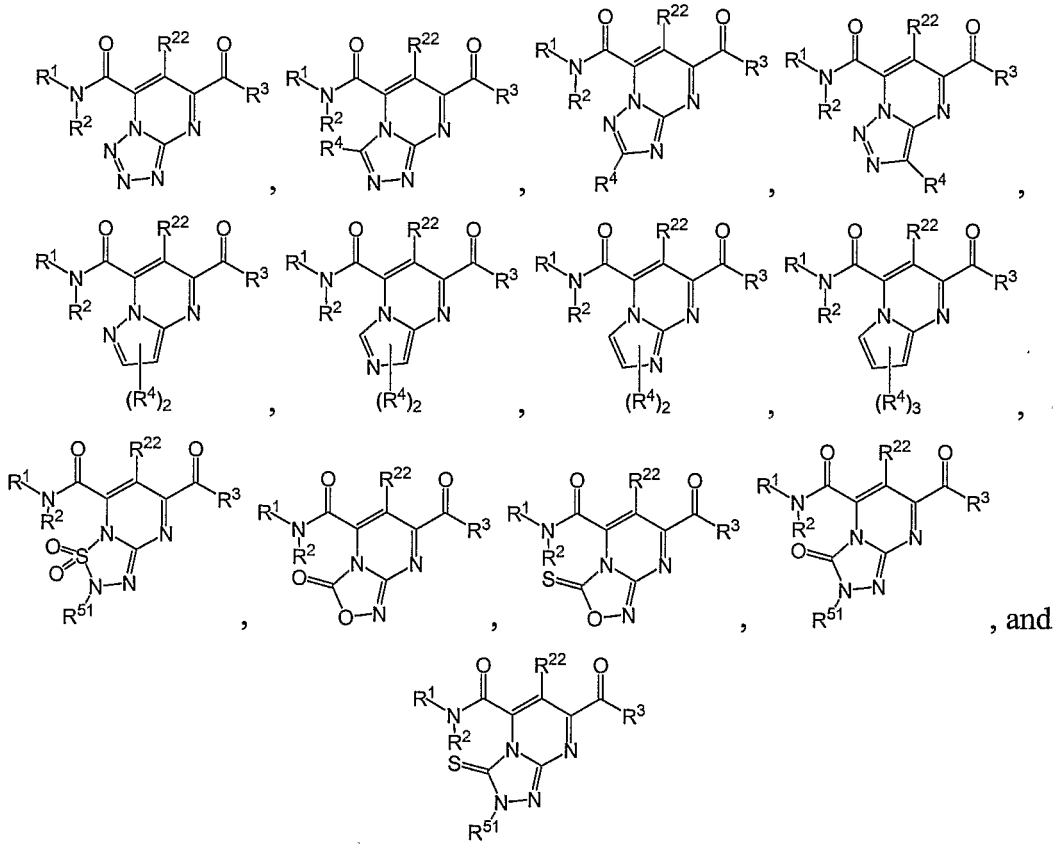
D is a member selected from the group consisting of CR^{22} and N;

x is selected from 0 to 2;

y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

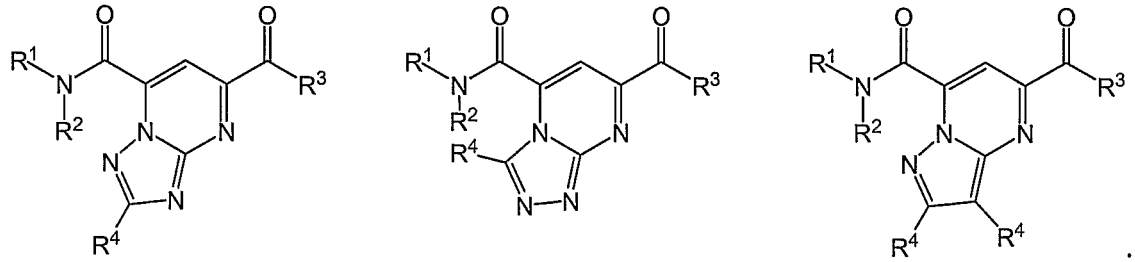
32. The compound of claim 31, selected from the group consisting of:



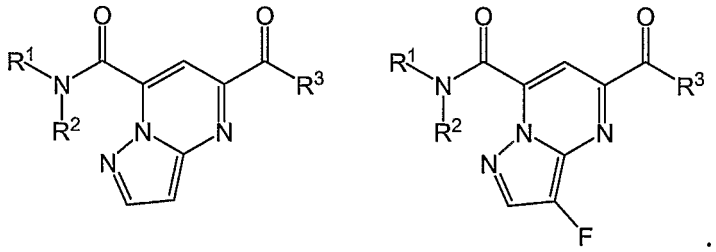
wherein:

R^{51} is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and haloalkyl, wherein alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and haloalkyl are optionally substituted one or more times.

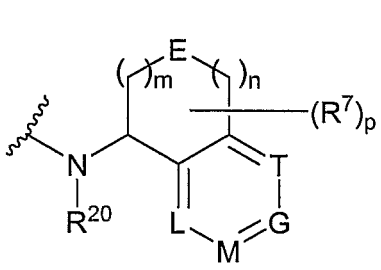
33. The compound of claim 32, selected from the group consisting of:



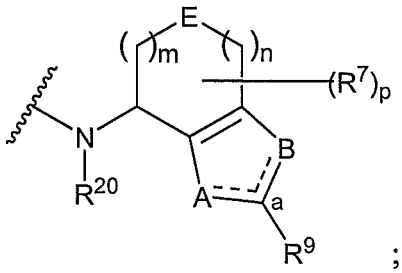
34. The compound of claim 33, selected from the group consisting of:



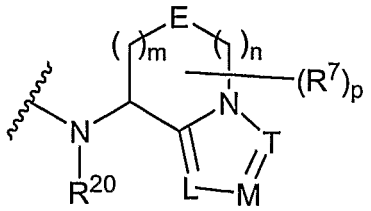
35. The compound of claim 32, wherein R^3 is selected from the group consisting of:



;



; and



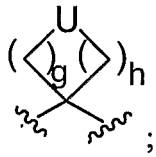
wherein:

R^5 is independently selected from the group consisting of hydrogen, alkyl, $C(O)NR^{10}R^{11}$, aryl, arylalkyl, $SO_2NR^{10}R^{11}$ and $C(O)OR^{10}$ wherein alkyl, aryl and arylalkyl are optionally substituted one or more times;

R^7 is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, halo, R^4 and $NR^{10}R^{11}$, wherein alkyl and cycloalkyl are optionally substituted one or more times, or optionally two R^7 groups together at the same carbon atom form =O, =S or $=NR^{10}$;

R^9 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, CHF_2, CF_3, OR^{10}, $COOR^{10}$, $CH(CH_3)CO_2H$, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$P(O)_2OH$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=N\text{-}CN)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=N\text{-}CN)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=N\text{-}NO_2)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=N\text{-}NO_2)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2NR^{10}$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2NR^{10}$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $S(O)_2NR^{10}$-alkyl, $S(O)_2$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $(C_0\text{-}C_6)$-alkyl-C(O)-NR^{11}-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{11}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

E is selected from the group consisting of a bond, $CR^{10}R^{11}$, O, NR^5, S, S=O, $S(=O)_2$, C(=O), $N(R^{10})(C=O)$, $(C=O)N(R^{10})$, $N(R^{10})S(=O)_2$, $S(=O)_2N(R^{10})$, C=N-OR^{11}, $-C(R^{10}R^{11})C(R^{10}R^{11})-$, $-CH_2-W^1-$ and



;

W^1 is selected from the group consisting of O, NR^5, S, S=O, $S(=O)_2$, $N(R^{10})(C=O)$, $N(R^{10})S(=O)_2$ and $S(=O)_2N(R^{10})$;

U is selected from the group consisting of $C(R^5R^{10})$, NR^5, O, S, S=O and $S(=O)_2$;

A and B are independently selected from the group consisting of CR^9, CR^9R^{10}, NR^{10}, N, O and S;

G, L, M and T are independently selected from the group consisting of CR^9 and N;

g and h are independently selected from 0-2;

m and n are independently selected from 0-3, provided that:

(1) when E is present, m and n are not both 3;

(2) when E is $-CH_2-W^1-$, m and n are not 3; and

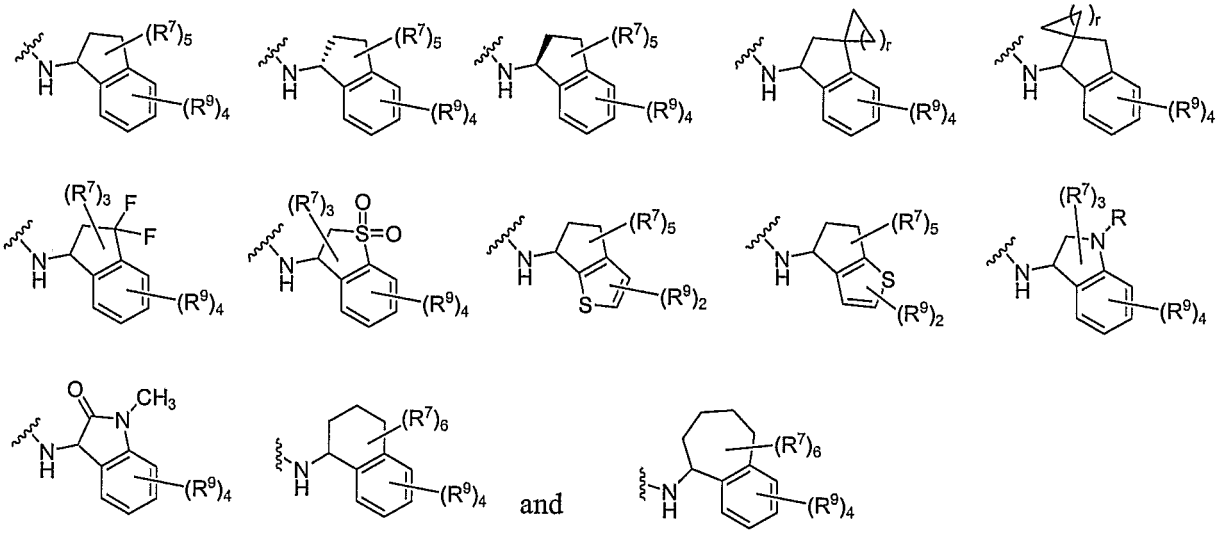
(3) when E is a bond, m and n are not 0;

p is selected from 0-6;

y is selected from 1 and 2; and

wherein the dotted line represents a double bond between one of: carbon "a" and A, or carbon "a" and B.

36. The compound according to claim 35, wherein R^3 is selected from the group consisting of:

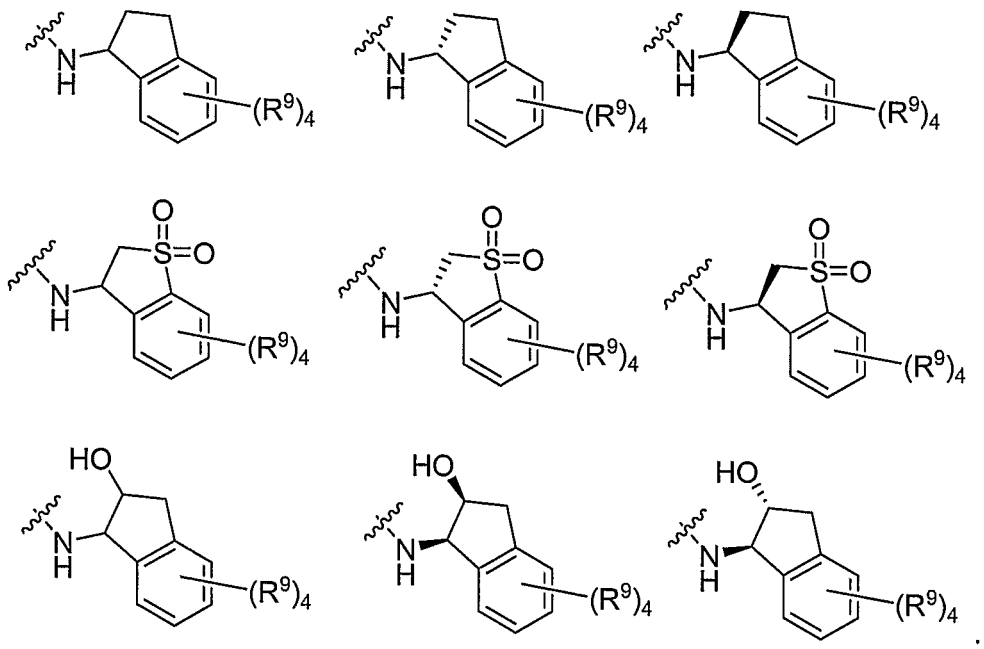


wherein:

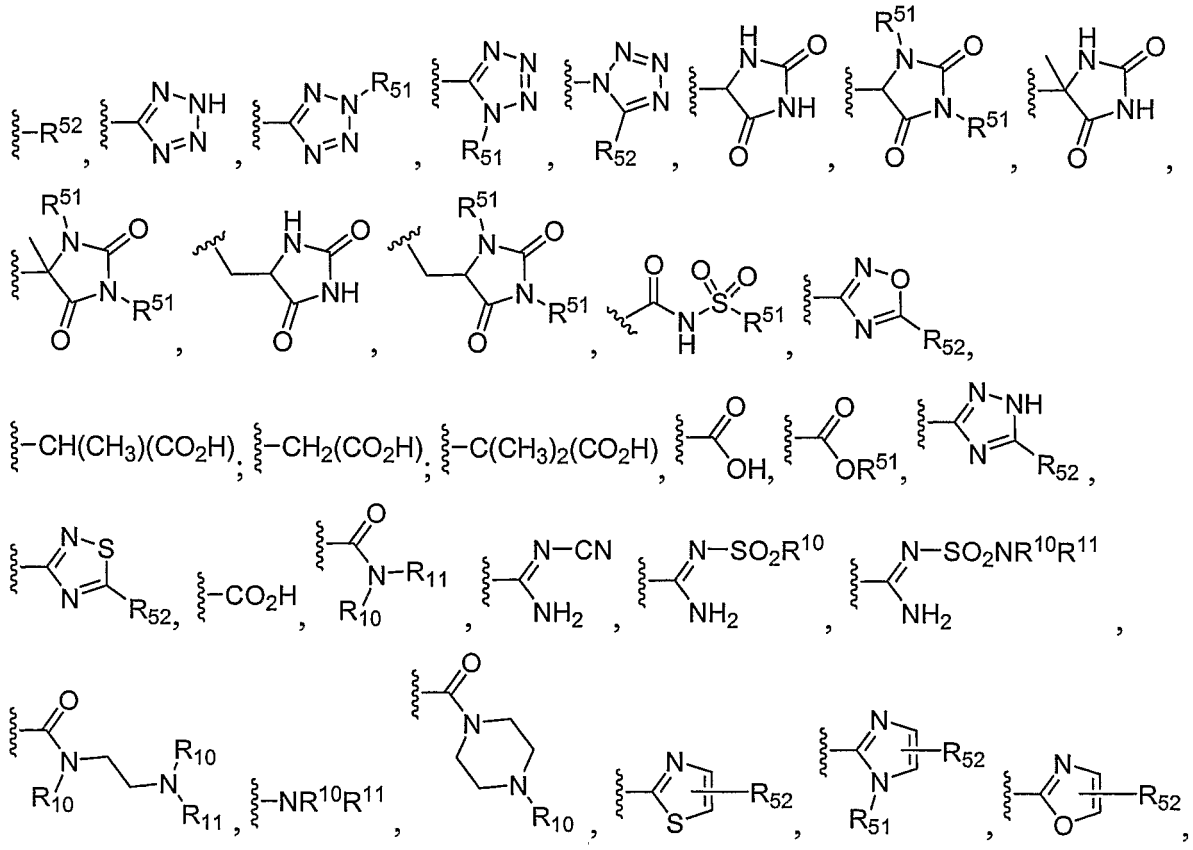
R is selected from the group consisting of $C(O)NR^{10}R^{11}$, COR^{10}, $SO_2NR^{10}R^{11}$, SO_2R^{10}, $CONHCH_3$ and $CON(CH_3)_2$, wherein $C(O)NR^{10}R^{11}$, COR^{10}, $SO_2NR^{10}R^{11}$, SO_2R^{10}, $CONHCH_3$ and $CON(CH_3)_2$ are optionally substituted one or more times; and

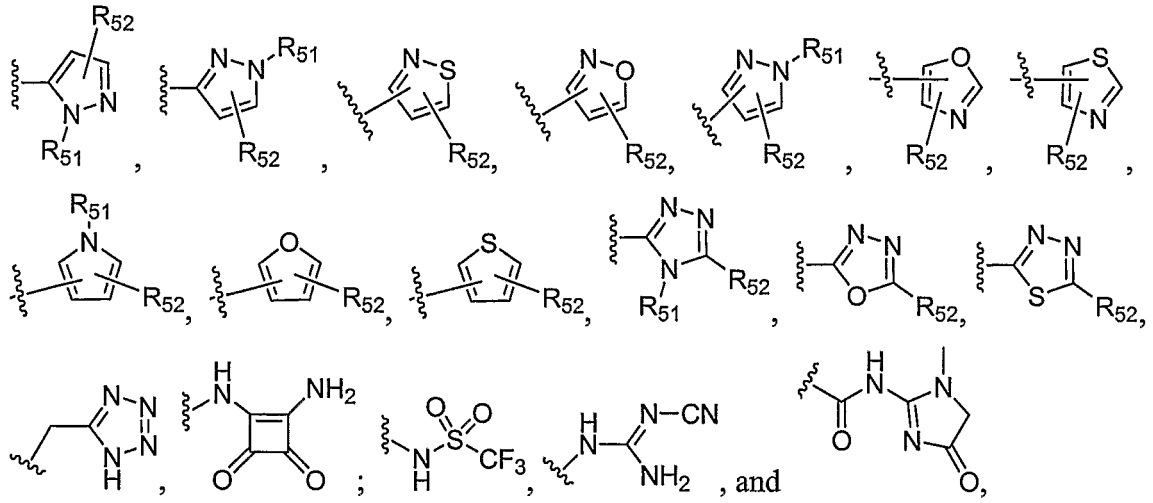
r is selected from 1-4.

37. The compound according to claim 35, wherein R^3 is selected from the group consisting of:



38. The compound according to claim 37, wherein R^9 is selected from the group consisting of:

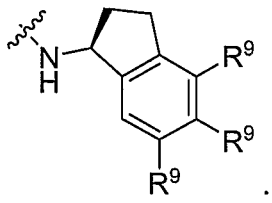




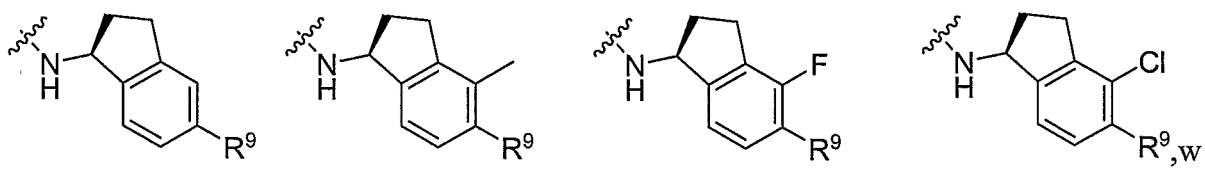
wherein:

R^{52} is selected from the group consisting of hydrogen, halo, CN, hydroxy, alkoxy, fluoroalkoxy, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, haloalkyl, $C(O)NR^{10}R^{11}$ and $SO_2NR^{10}R^{11}$, wherein alkoxy, fluoroalkoxy, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, and haloalkyl are optionally substituted one or more times.

39. The compound according to claim 37, wherein R^3 is

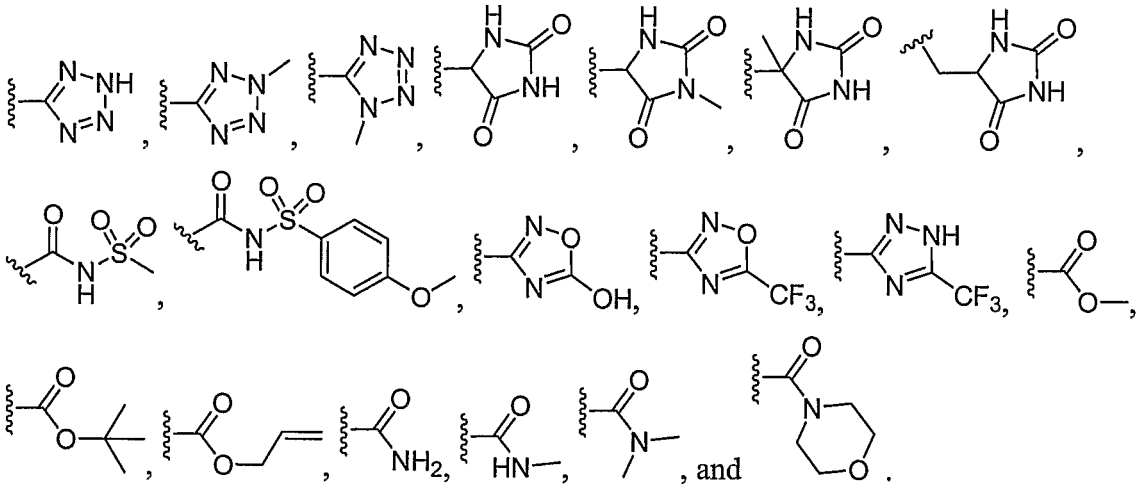


40. The compound according to claim 39, wherein R^3 is selected from the group consisting of:

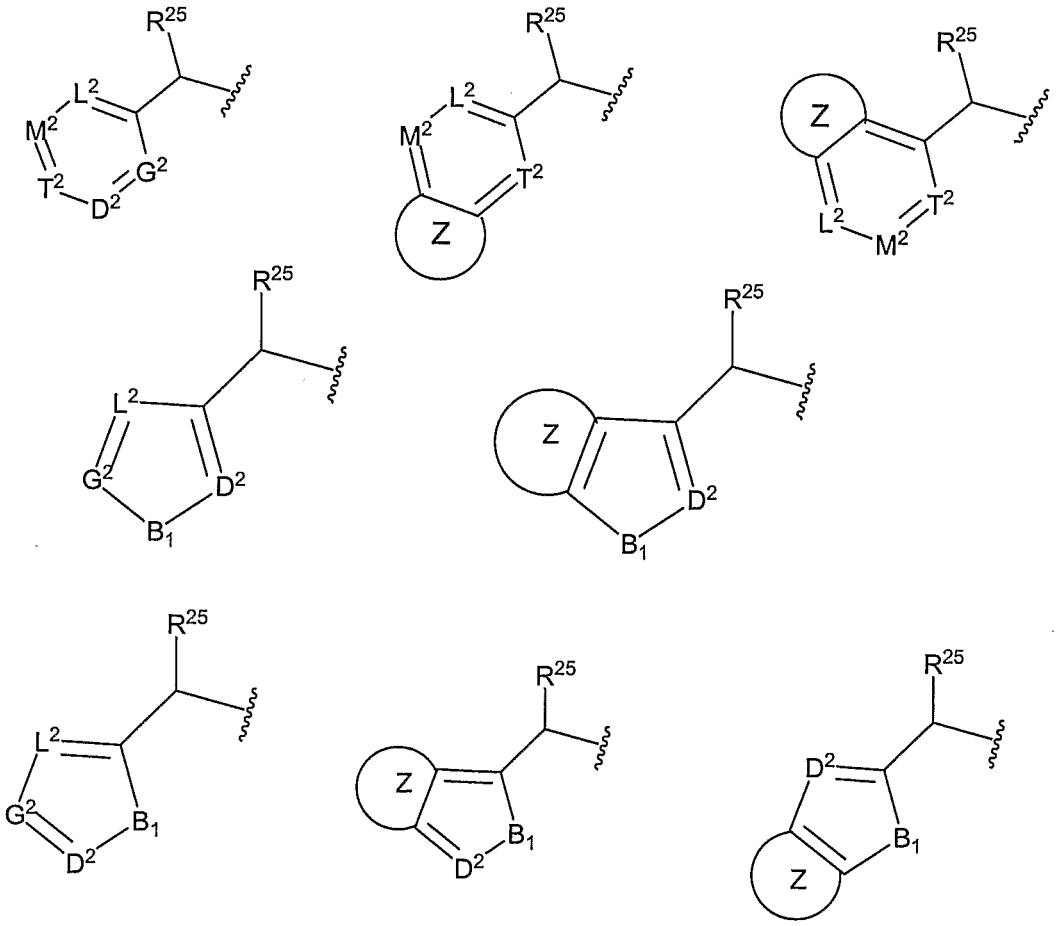


herein:

R^9 is selected from the group consisting of hydrogen, fluoro, halo, CN, alkyl, CO_2H,



41. The compound according to claim 32, wherein R^1 is selected from the group consisting of:



wherein:

R^{18} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl are optionally substituted one or more times;

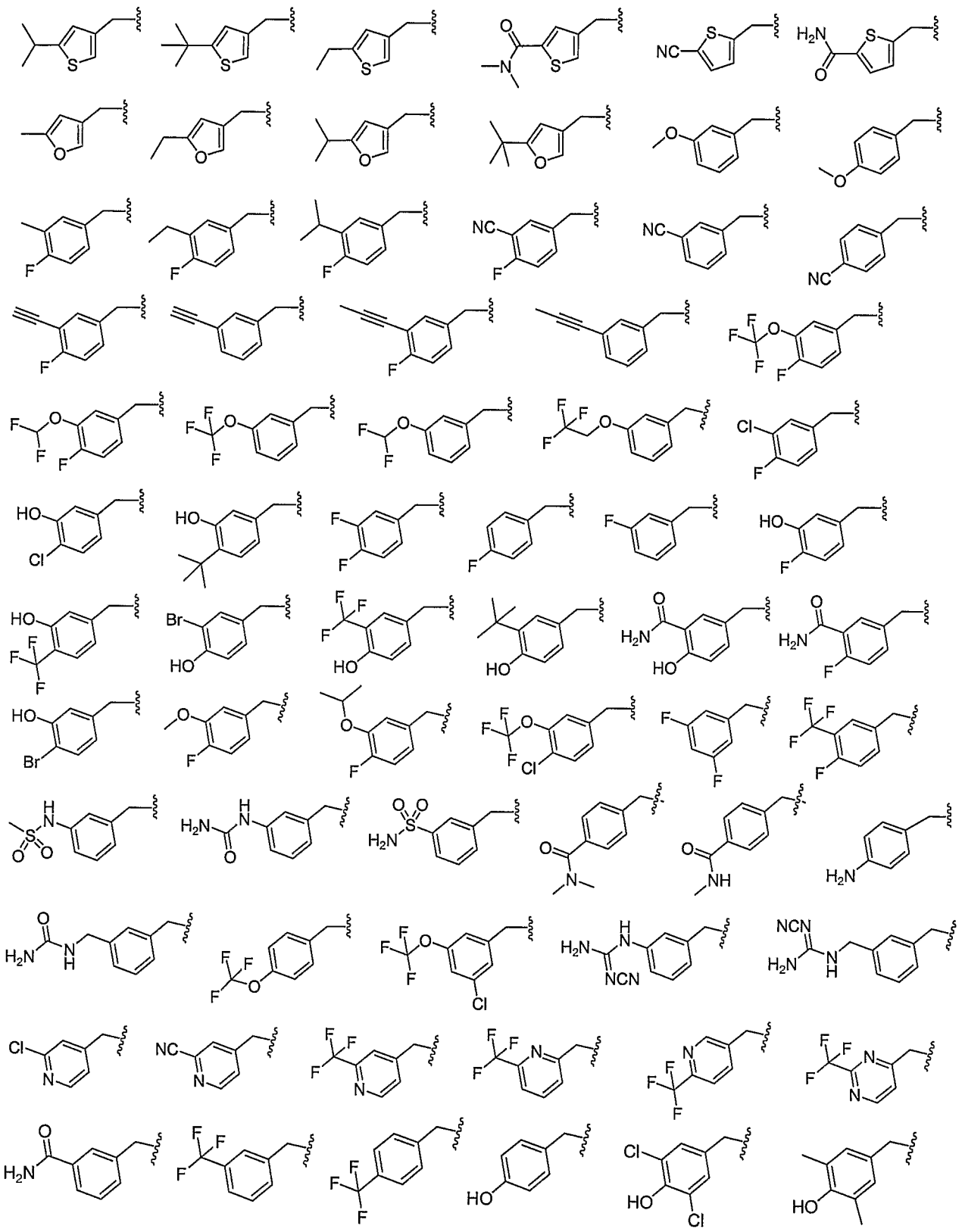
R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $C(O)NR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

B_1 is selected from the group consisting of NR^{10}, O and S;

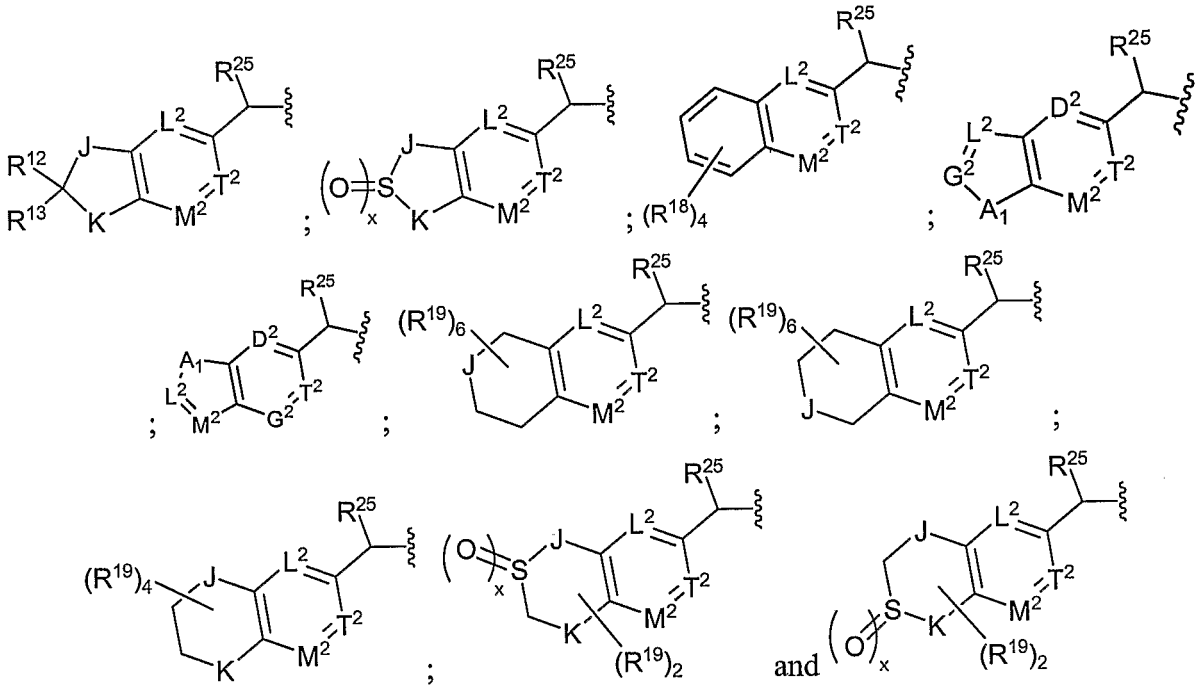
D^2, G^2, L^2, M^2 and T^2 are independently selected from the group consisting of CR^{18} and N; and

Z is a 5- to 8-membered ring selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted one or more times.

42. The compound according to claim 41, wherein R^1 is selected from the group consisting of:



43. The compound of claim 32, wherein R^1 is selected from the group consisting of:



wherein:

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, alkyl and halo, wherein alkyl is optionally substituted one or more times, or optionally R^{12} and R^{13} together form =O, =S or $=NR^{10}$;

R^{18} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{19} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two R^{19} groups together at one carbon atom form =O, =S or $=NR^{10}$;

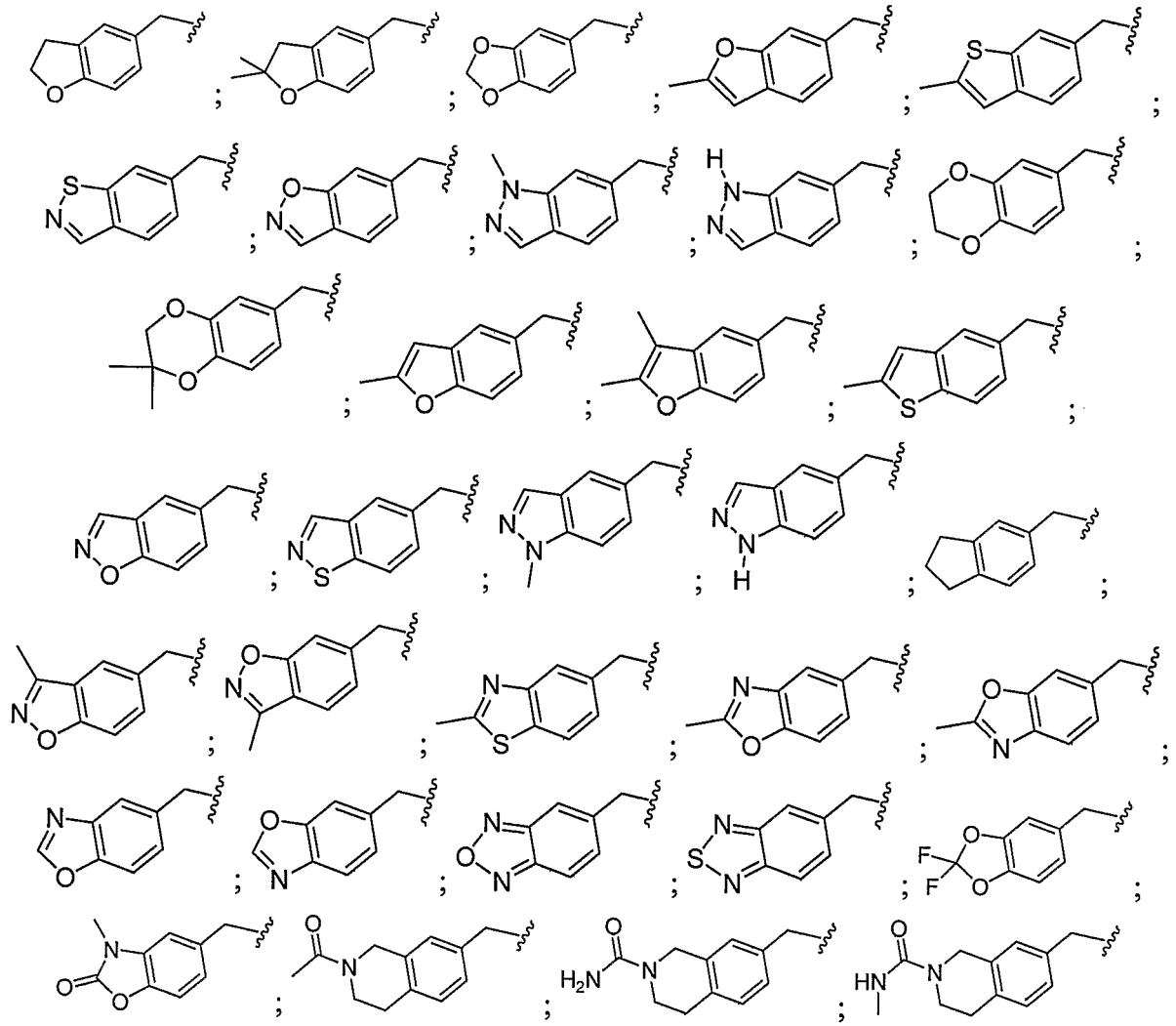
R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $C(O)NR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

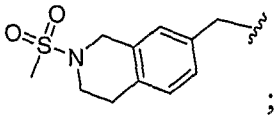
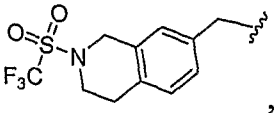
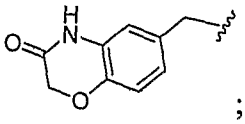
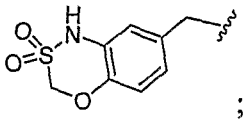
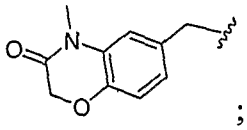
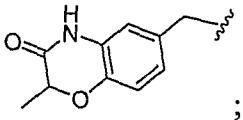
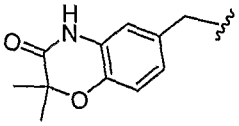
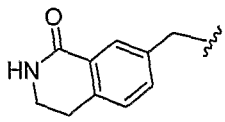
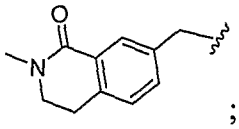
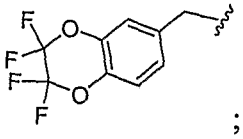
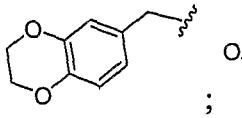
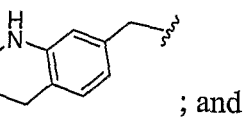
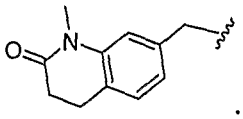
J and K are independently selected from the group consisting of $CR^{10}R^{18}$, NR^{10}, O and $S(O)_x$;

A_1 is selected from the group consisting of NR^{10}, O and S;

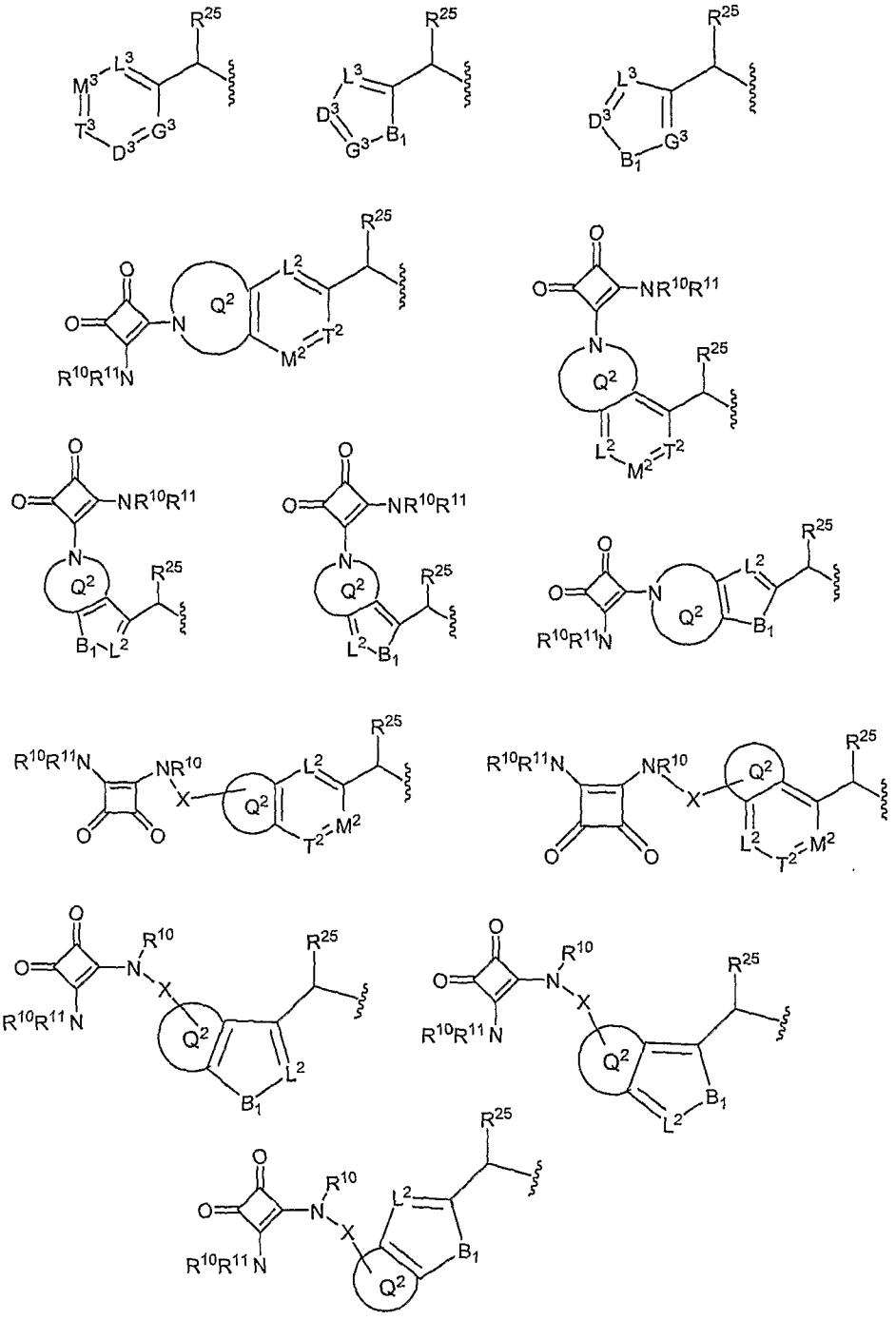
D^2, G^2, L^2, M^2 and T^2 are independently selected from the group consisting of CR^{18} and N.

44. The compound of claim 43, wherein R^1 is selected from the group consisting of:




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; and

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45. The compound of claim 32, wherein R^1 is selected from the group consisting of:



wherein:

R^5 is independently selected from the group consisting of hydrogen, alkyl, $C(O)NR^{10}R^{11}$, aryl, arylalkyl, $SO_2NR^{10}R^{11}$ and $C(O)OR^{10}$ wherein alkyl, aryl and arylalkyl are optionally substituted one or more times;

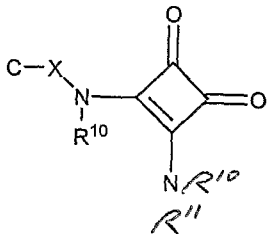
R^{18} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{19} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two R^{19} groups together at one carbon atom form =O, =S or $=NR^{10}$;

R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $CONR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl and haloalkyl are optionally substituted one or more times;

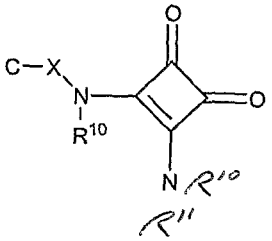
L^2, M^2, and T^2 are independently selected from the group consisting of CR^{18} and N;

L^3, M^3, T^3, D^3, and G^3 are independently selected from N, CR^{18}, and



,

with the provision that one of L^3, M^3, T^3, D^3, and G^3 is

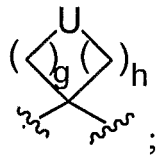


;

B_1 is selected from the group consisting of NR^{10}, O and S;

X is selected from the group consisting of a bond and $(CR^{10}R^{11})_wE(CR^{10}R^{11})_w$

E is selected from the group consisting of a bond, $CR^{10}R^{11}$, O, NR^5, S, S=O, $S(=O)_2$, C(=O), $N(R^{10})(C=O)$, $(C=O)N(R^{10})$, $N(R^{10})S(=O)_2$, $S(=O)_2N(R^{10})$, C=N-OR^{11}, $-C(R^{10}R^{11})C(R^{10}R^{11})-$, $-CH_2-W^1-$ and



;

W^1 is selected from the group consisting of O, NR^5, S, S=O, $S(=O)_2$, $N(R^{10})(C=O)$, $N(R^{10})S(=O)_2$ and $S(=O)_2N(R^{10})$;

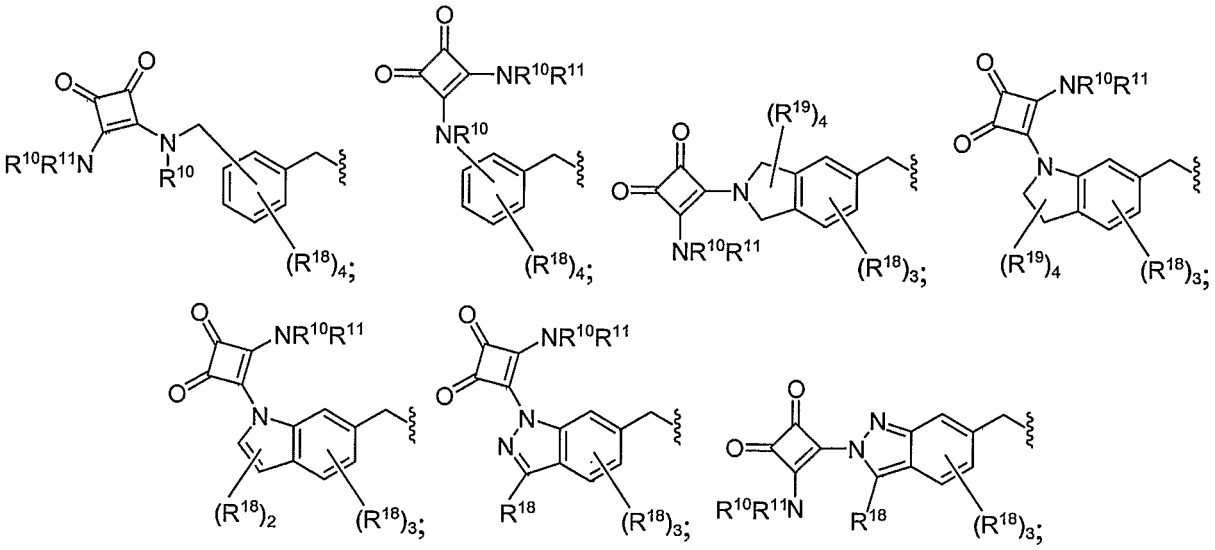
U is selected from $C(R^5R^{10})$, NR^5, O, S, S=O, $S(=O)_2$;

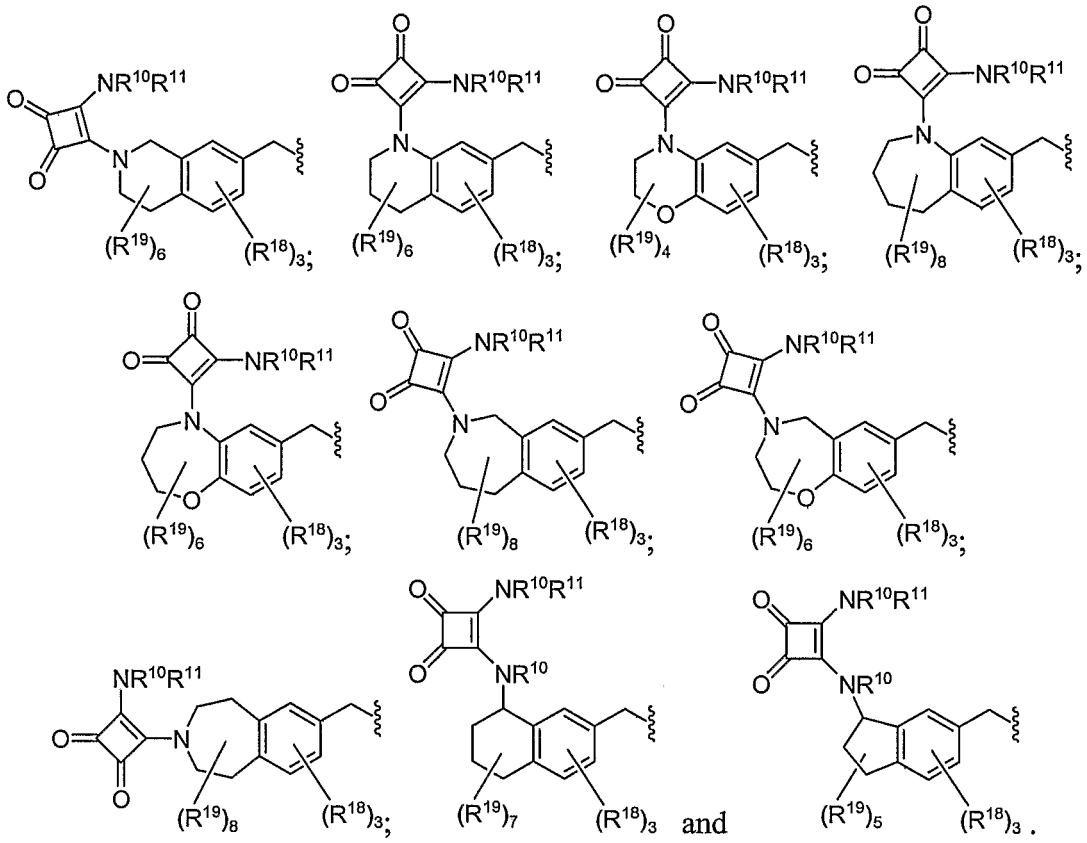
g and h are independently selected from 0-2;

w is selected from 0-4; and

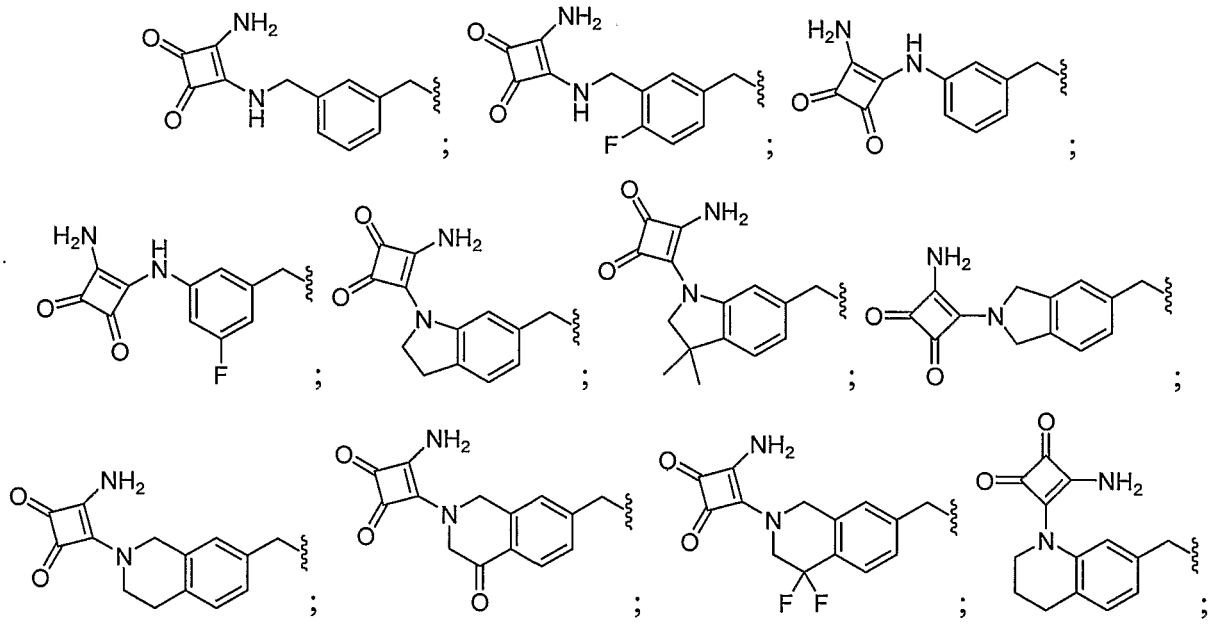
Q^2 is a 5- to 8-membered ring consisting of cycloalkyl, heterocycloalkyl, aryl, heteroaryl, which is optionally substituted one or more times with R^{19}.

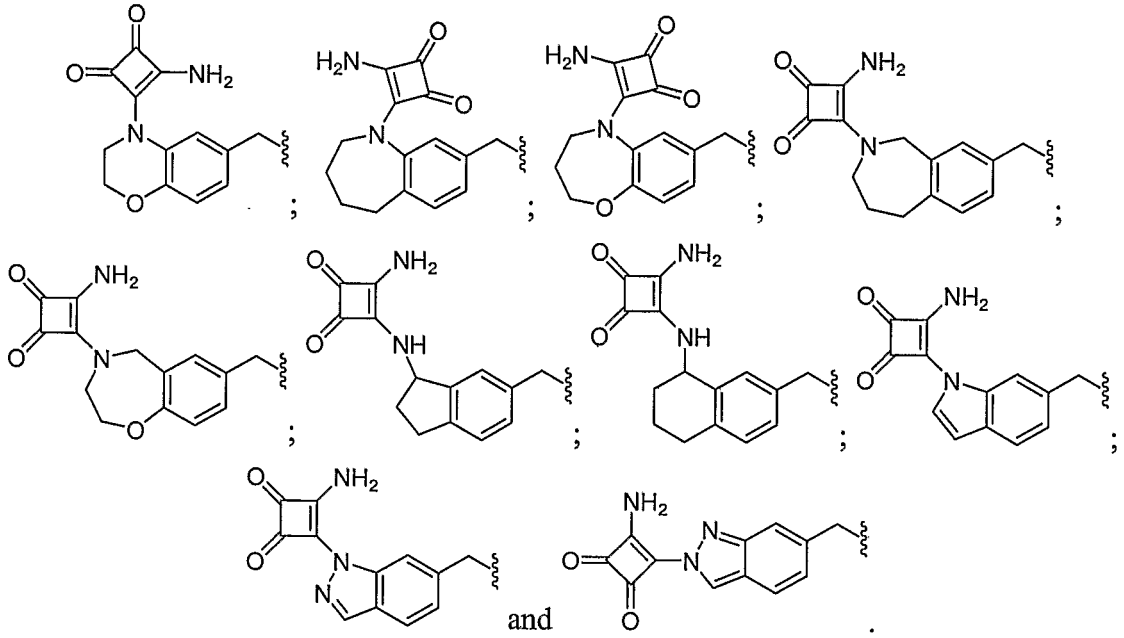
46. The compound of claim 45, wherein R^1 is selected from the group consisting of:



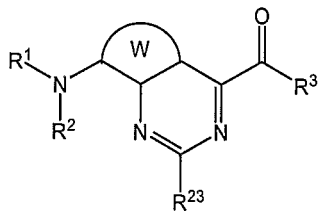


47. The compound of claim 46, wherein R^1 is selected from the group consisting of:





48. A compound having Formula (IV):



Formula (IV)

wherein:

R^1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused

heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^3 is $NR^{20}R^{21}$;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-C(O)-NR^{11}-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and

optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{20} is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted;

R^{21} is a bicyclic or tricyclic fused ring system, wherein at least one ring is partially saturated, and wherein the bicyclic or tricyclic fused ring system is optionally substituted;

R^{23} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N{=}CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{30} is selected from the group consisting of alkyl and $(C_0\text{-}C_6)$-alkyl-aryl, wherein alkyl and aryl are optionally substituted;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$ are optionally substituted;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted;

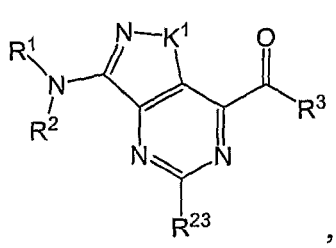
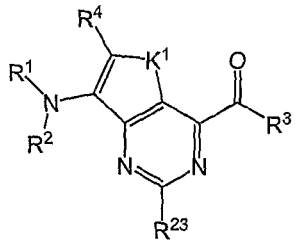
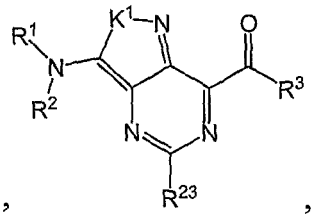
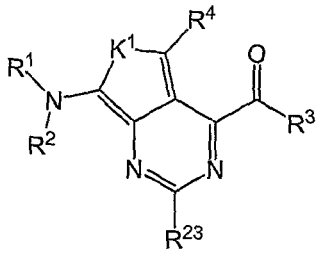
W is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

x is selected from 0 to 2;

y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

49. The compound of claim 48, selected from the group consisting of:

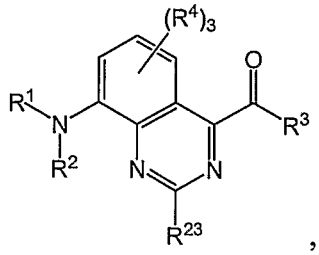
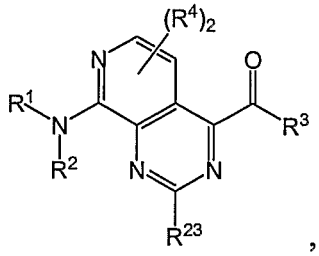
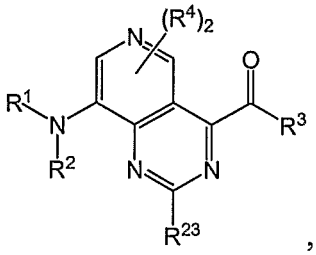
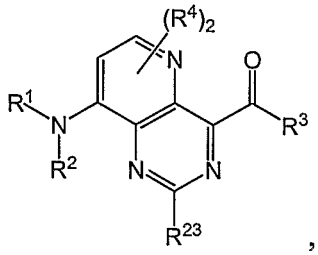
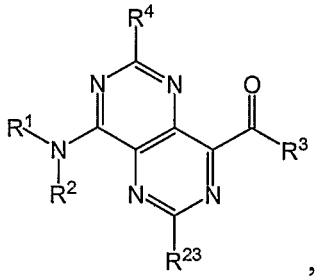
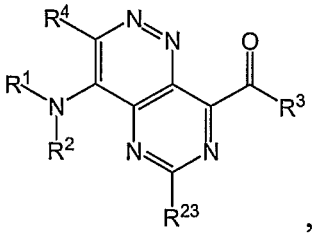
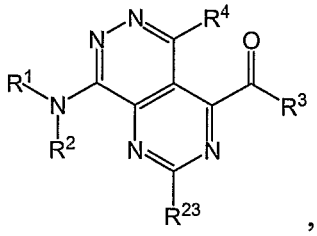
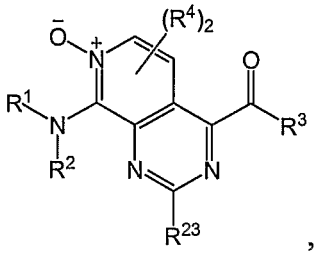
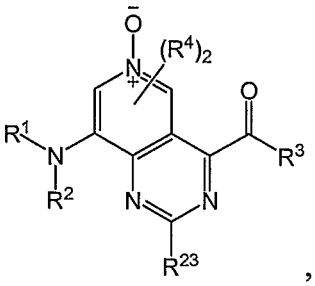
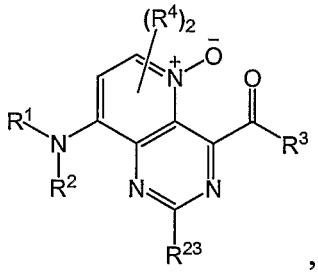
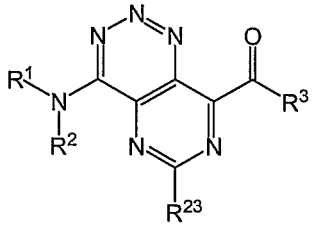

,

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, and


wherein:

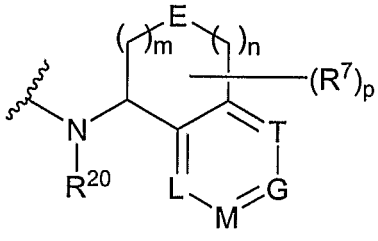
K^1 is O, S, or NR^{51}; and

R^{51} is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and haloalkyl, wherein alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and haloalkyl are optionally substituted one or more times.

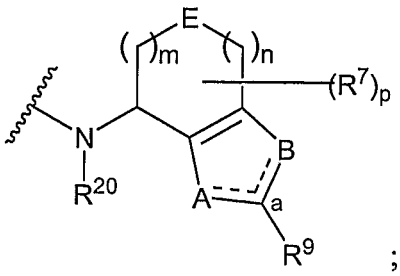
50. The compound of claim 48, selected from the group consisting of:


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, and

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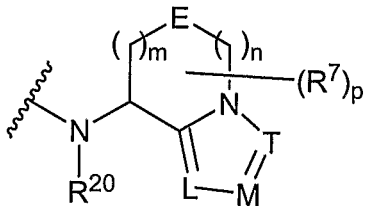
51. The compound of claim 48, wherein R^3 is selected from the group consisting of:



;



; and



wherein:

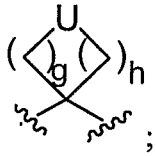
R^5 is independently selected from the group consisting of hydrogen, alkyl, $C(O)NR^{10}R^{11}$, aryl, arylalkyl, $SO_2NR^{10}R^{11}$ and $C(O)OR^{10}$ wherein alkyl, aryl and arylalkyl are optionally substituted one or more times;

R^7 is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, halo, R^4 and $NR^{10}R^{11}$, wherein alkyl and cycloalkyl are optionally substituted one or more times, or optionally two R^7 groups together at the same carbon atom form =O, =S or $=NR^{10}$;

R^9 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, CHF_2, CF_3, OR^{10}, $COOR^{10}$, $CH(CH_3)CO_2H$, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$P(O)_2OH$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=N\text{-}CN)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=N\text{-}CN)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=N\text{-}NO_2)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=N\text{-}NO_2)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2NR^{10}$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2NR^{10}$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $S(O)_2NR^{10}$-alkyl, $S(O)_2$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $(C_0\text{-}C_6)$-alkyl-$C(O)\text{-}NR^{11}$-CN, O-$(C_0\text{-}C_6)$-

alkyl-C(O)$NR^{10}R^{11}$, $S(O)_x$-(C_0-C_6)-alkyl-C(O)OR^{10}, $S(O)_x$-(C_0-C_6)-alkyl-C(O)$NR^{10}R^{11}$, (C_0-C_6)-alkyl-C(O)NR^{10}-(C_0-C_6)-alkyl-$NR^{10}R^{11}$, (C_0-C_6)-alkyl-NR^{10}-C(O)R^{10}, (C_0-C_6)-alkyl-NR^{10}-C(O)OR^{10}, (C_0-C_6)-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, (C_0-C_6)-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, (C_0-C_6)-alkyl-NR^{10}-$S(O)_yR^{11}$, O-(C_0-C_6)-alkyl-aryl and O-(C_0-C_6)-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

E is selected from the group consisting of a bond, $CR^{10}R^{11}$, O, NR^5, S, S=O, $S(=O)_2$, C(=O), $N(R^{10})$(C=O), (C=O)$N(R^{10})$, $N(R^{10})S(=O)_2$, $S(=O)_2N(R^{10})$, C=N-OR^{11}, -$C(R^{10}R^{11})C(R^{10}R^{11})$-, -$CH_2$-$W^1$- and



;

W^1 is selected from the group consisting of O, NR^5, S, S=O, $S(=O)_2$, $N(R^{10})$(C=O), $N(R^{10})S(=O)_2$ and $S(=O)_2N(R^{10})$;

U is selected from the group consisting of $C(R^5R^{10})$, NR^5, O, S, S=O and $S(=O)_2$;

A and B are independently selected from the group consisting of CR^9, CR^9R^{10}, NR^{10}, N, O and S;

G, L, M and T are independently selected from the group consisting of CR^9 and N;

g and h are independently selected from 0-2;

m and n are independently selected from 0-3, provided that:

(1) when E is present, m and n are not both 3;

(2) when E is -CH_2-W^1-, m and n are not 3; and

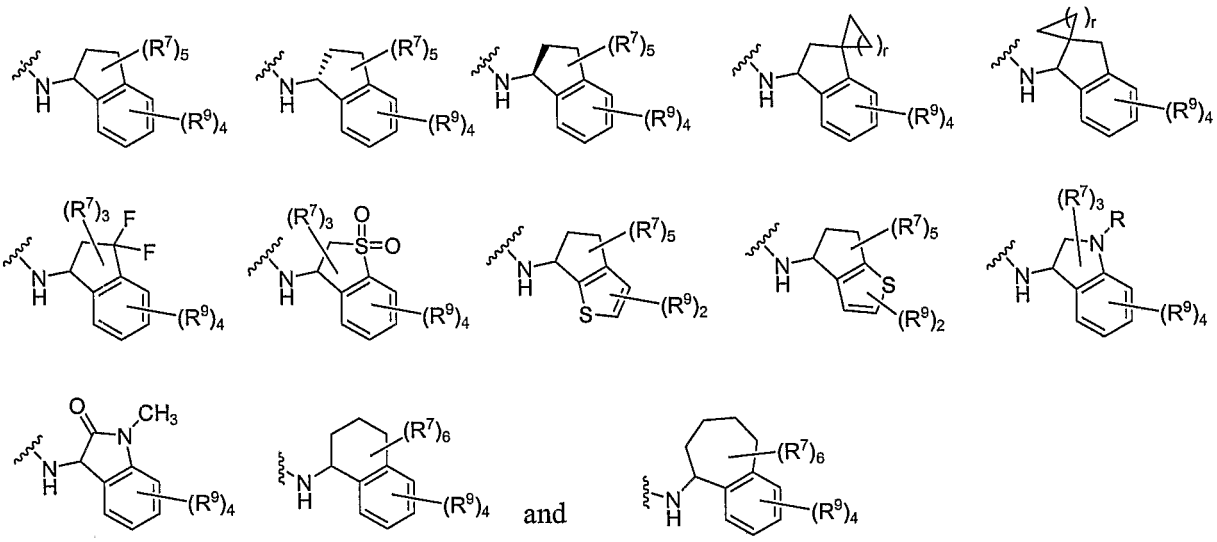
(3) when E is a bond, m and n are not 0;

p is selected from 0-6;

y is selected from 1 and 2; and

wherein the dotted line represents a double bond between one of: carbon "a" and A, or carbon "a" and B.

52. The compound according to claim 51, wherein R^3 is selected from the group consisting of:

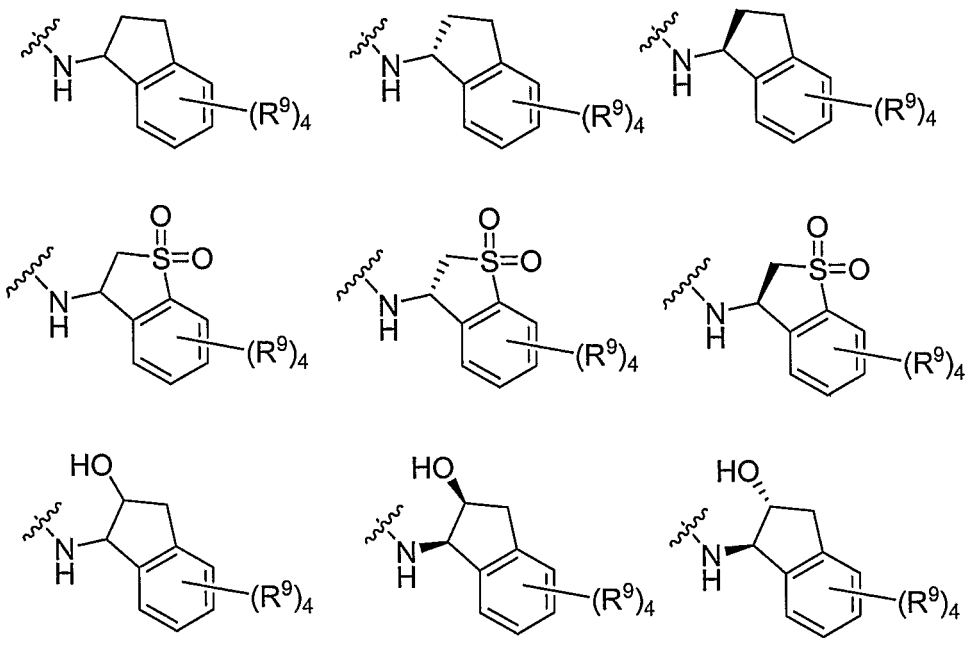


wherein:

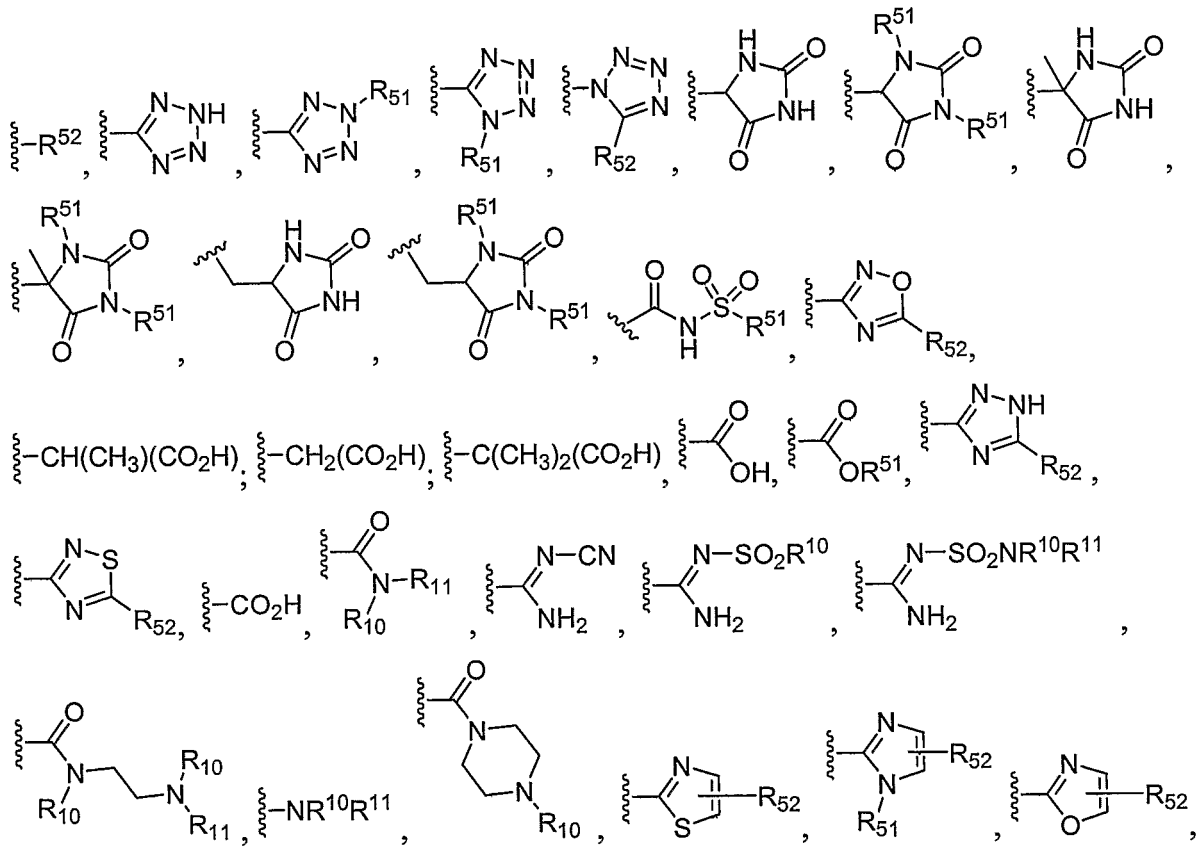
R is selected from the group consisting of $C(O)NR^{10}R^{11}$, COR^{10}, $SO_2NR^{10}R^{11}$, SO_2R^{10}, $CONHCH_3$ and $CON(CH_3)_2$, wherein $C(O)NR^{10}R^{11}$, COR^{10}, $SO_2NR^{10}R^{11}$, SO_2R^{10}, $CONHCH_3$ and $CON(CH_3)_2$ are optionally substituted one or more times; and

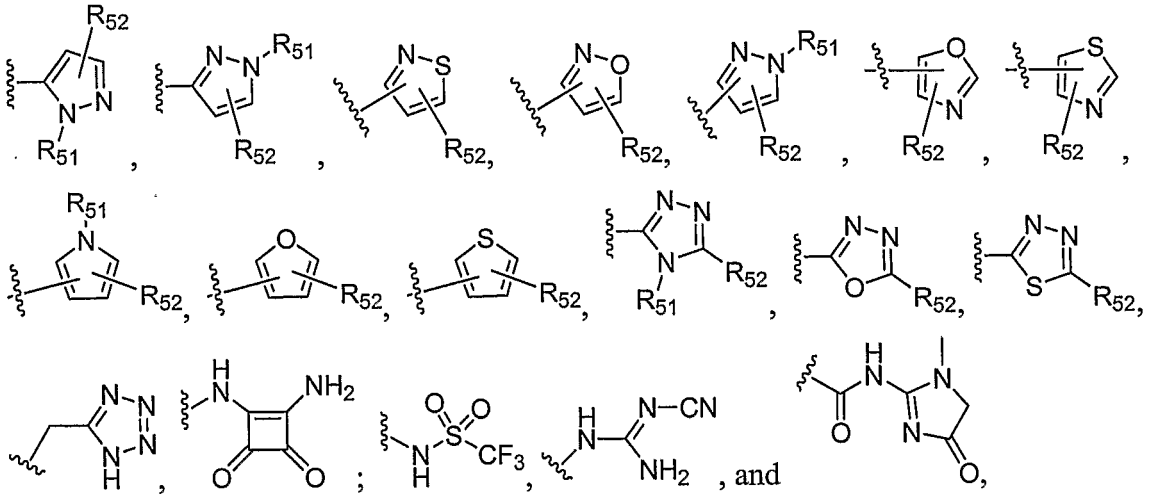
r is selected from 1-4.

53. The compound according to claim 51, wherein R^3 is selected from the group consisting of:



54. The compound according to claim 53, wherein R^9 is selected from the group consisting of:



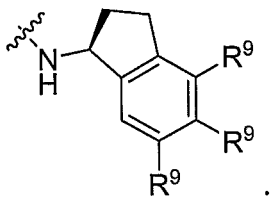


wherein:

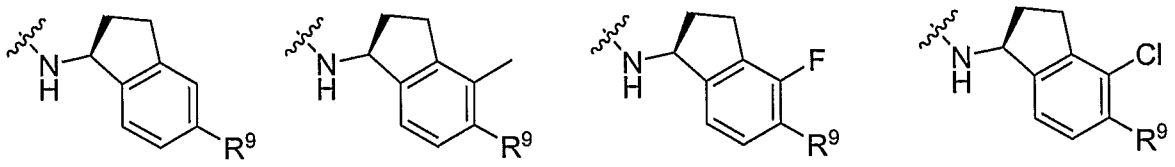
R^{51} is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and haloalkyl, wherein alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and haloalkyl are optionally substituted one or more times; and

R^{52} is selected from the group consisting of hydrogen, halo, CN, hydroxy, alkoxy, fluoroalkoxy, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, haloalkyl, $C(O)NR^{10}R^{11}$ and $SO_2NR^{10}R^{11}$, wherein alkoxy, fluoroalkoxy, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, and haloalkyl are optionally substituted one or more times.

55. The compound according to claim 51, wherein R^3 is:

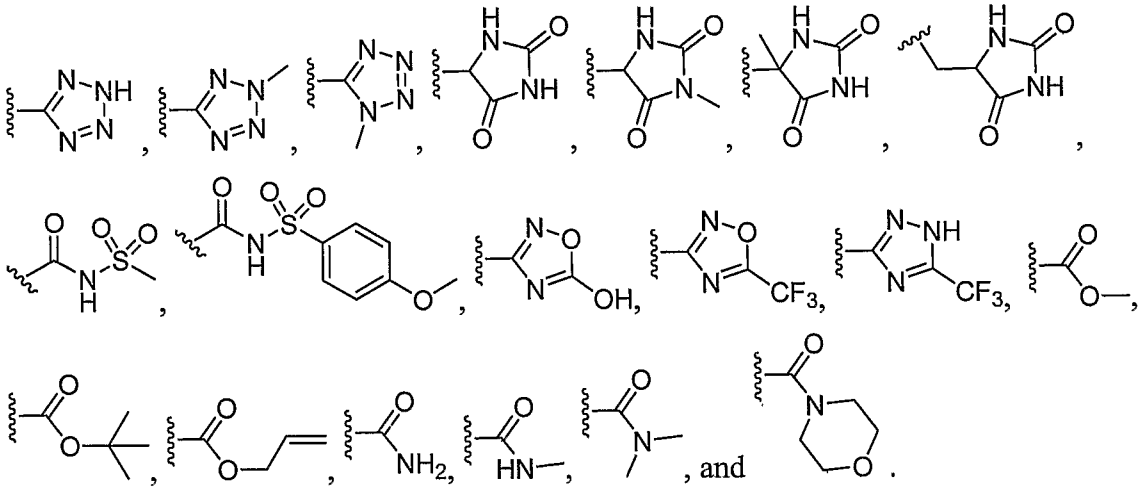


56. The compound according to claim 55, wherein R^3 is:

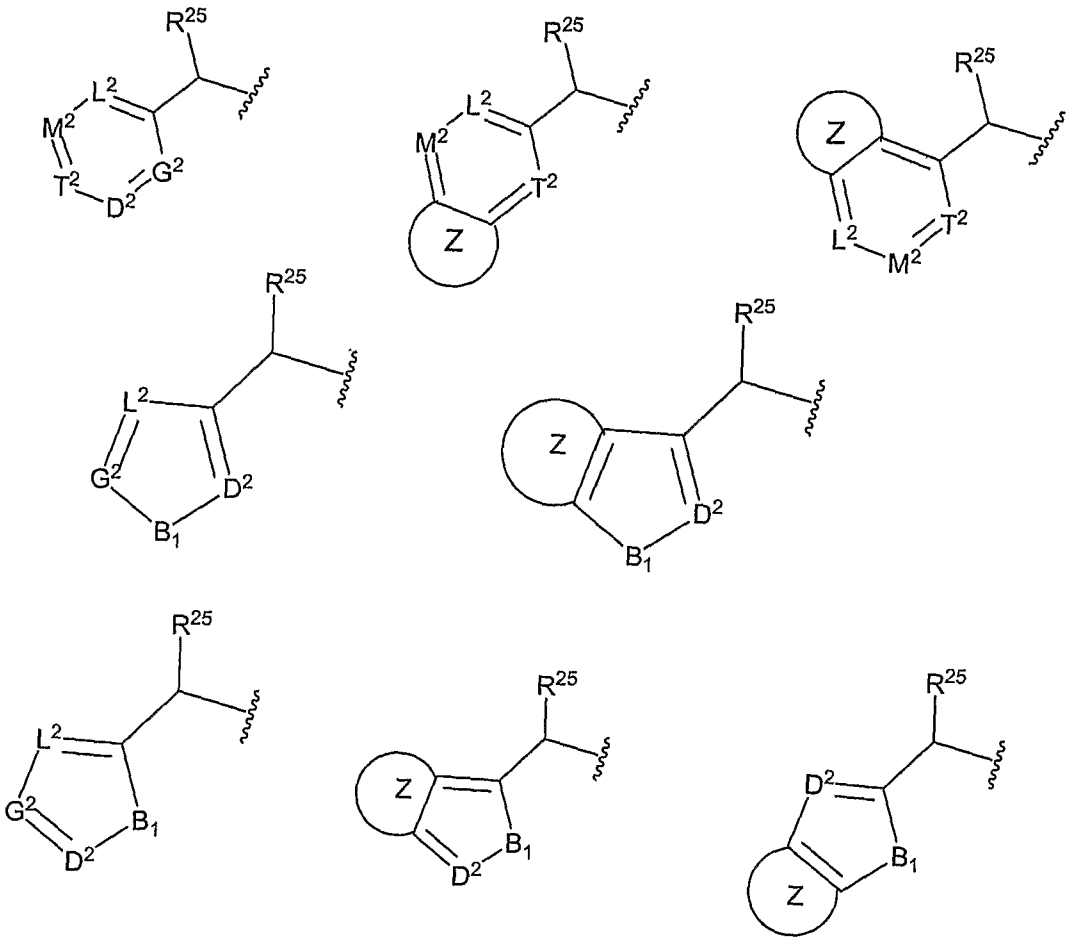


wherein:

R^9 is selected from the group consisting of hydrogen, fluoro, halo, CN, alkyl, CO_2H,



57. The compound according to claim 48, wherein R^1 is selected from the group consisting of:



wherein:

R^{18} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl are optionally substituted one or more times;

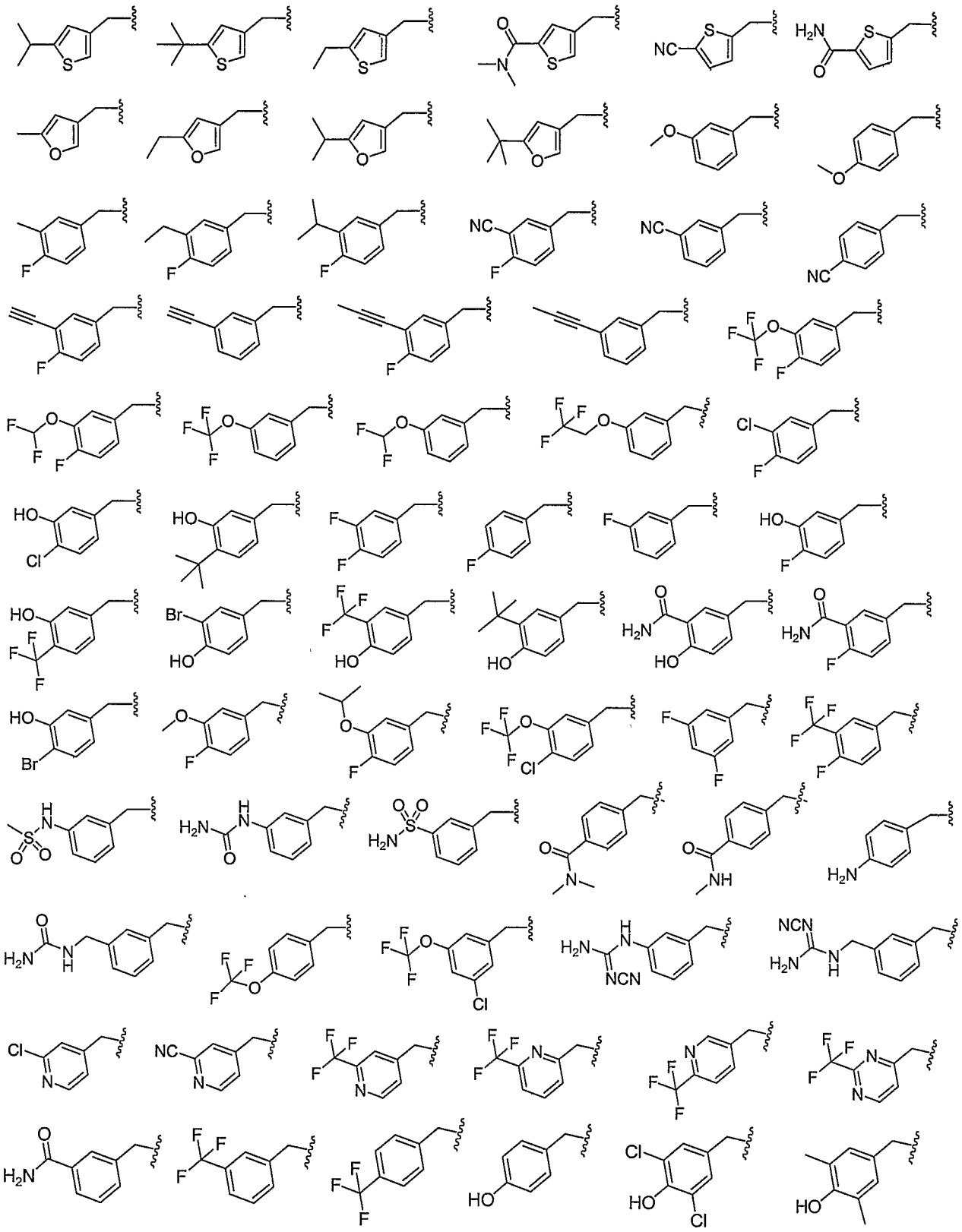
R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $C(O)NR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

B_1 is selected from the group consisting of NR^{10}, O and S;

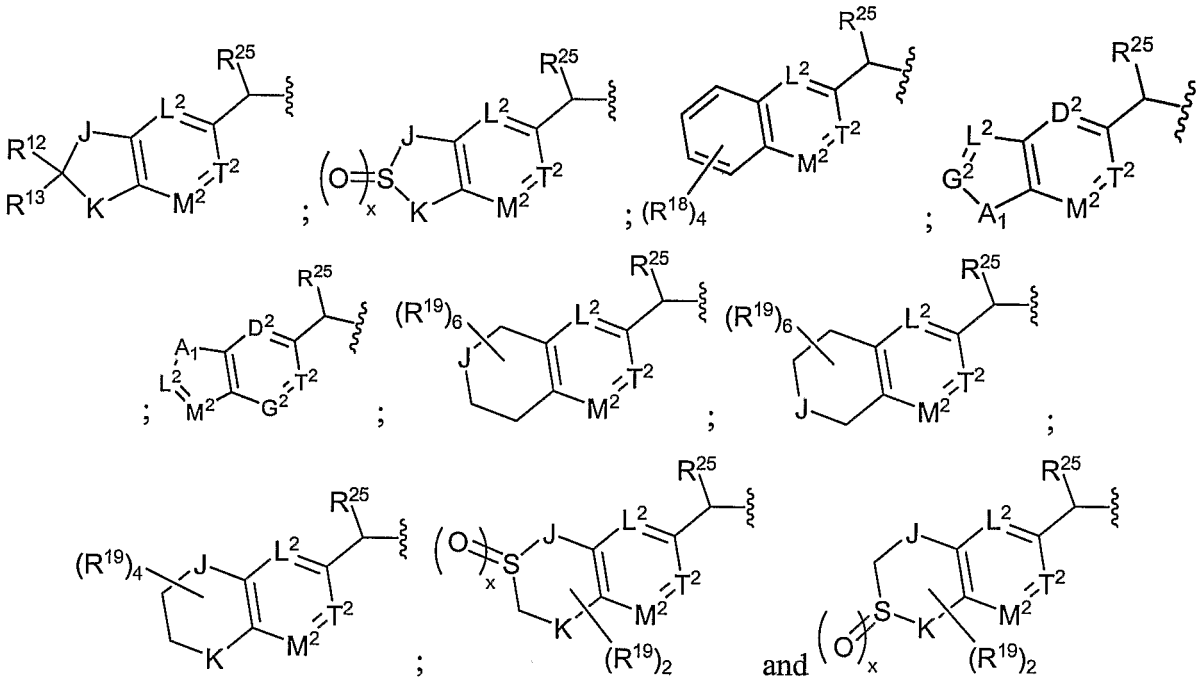
D^2, G^2, L^2, M^2 and T^2 are independently selected from the group consisting of CR^{18} and N; and

Z is a 5- to 8-membered ring selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted one or more times.

58. The compound according to claim 57, wherein R^1 is selected from the group consisting of:



59. The compound of claim 48, wherein R^1 is selected from the group consisting of:



wherein:

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, alkyl and halo, wherein alkyl is optionally substituted one or more times, or optionally R^{12} and R^{13} together form =O, =S or $=NR^{10}$;

R^{18} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{19} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two R^{19} groups together at one carbon atom form =O, =S or $=NR^{10}$;

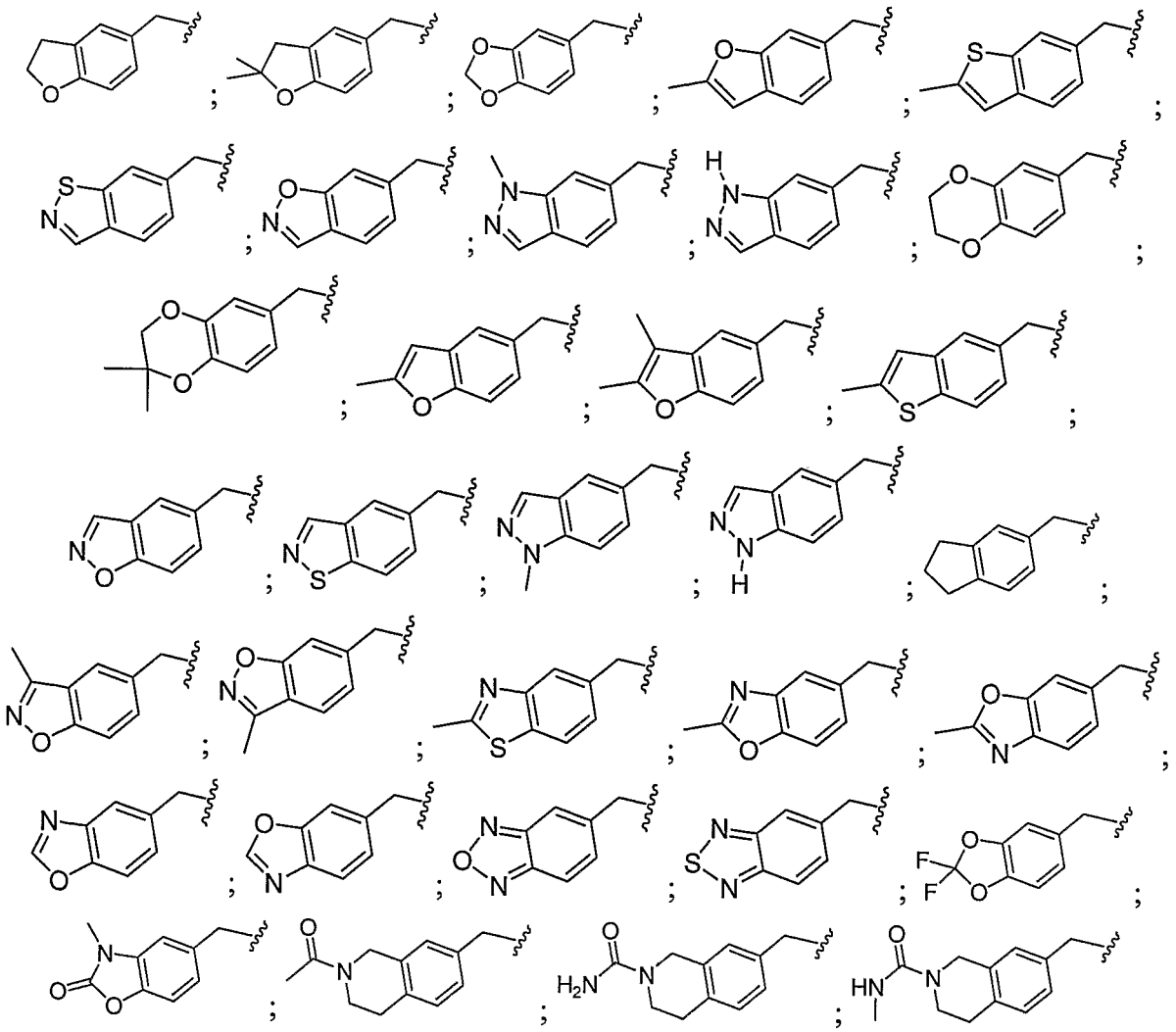
R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $C(O)NR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

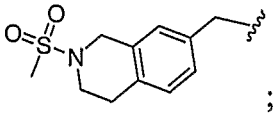
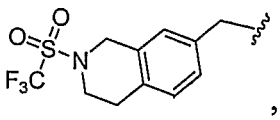
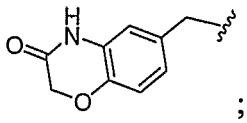
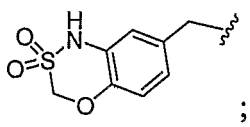
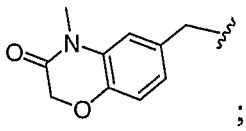
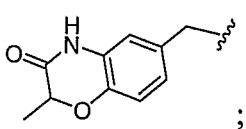
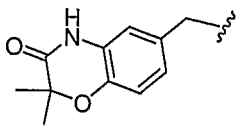
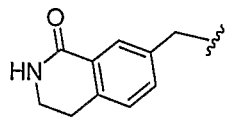
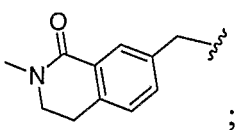
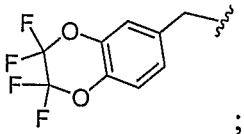
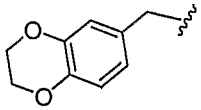
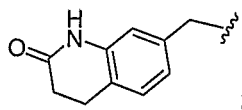
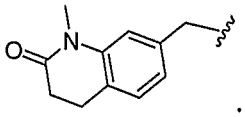
J and K are independently selected from the group consisting of $CR^{10}R^{18}$, NR^{10}, O and $S(O)_x$;

A_1 is selected from the group consisting of NR^{10}, O and S;

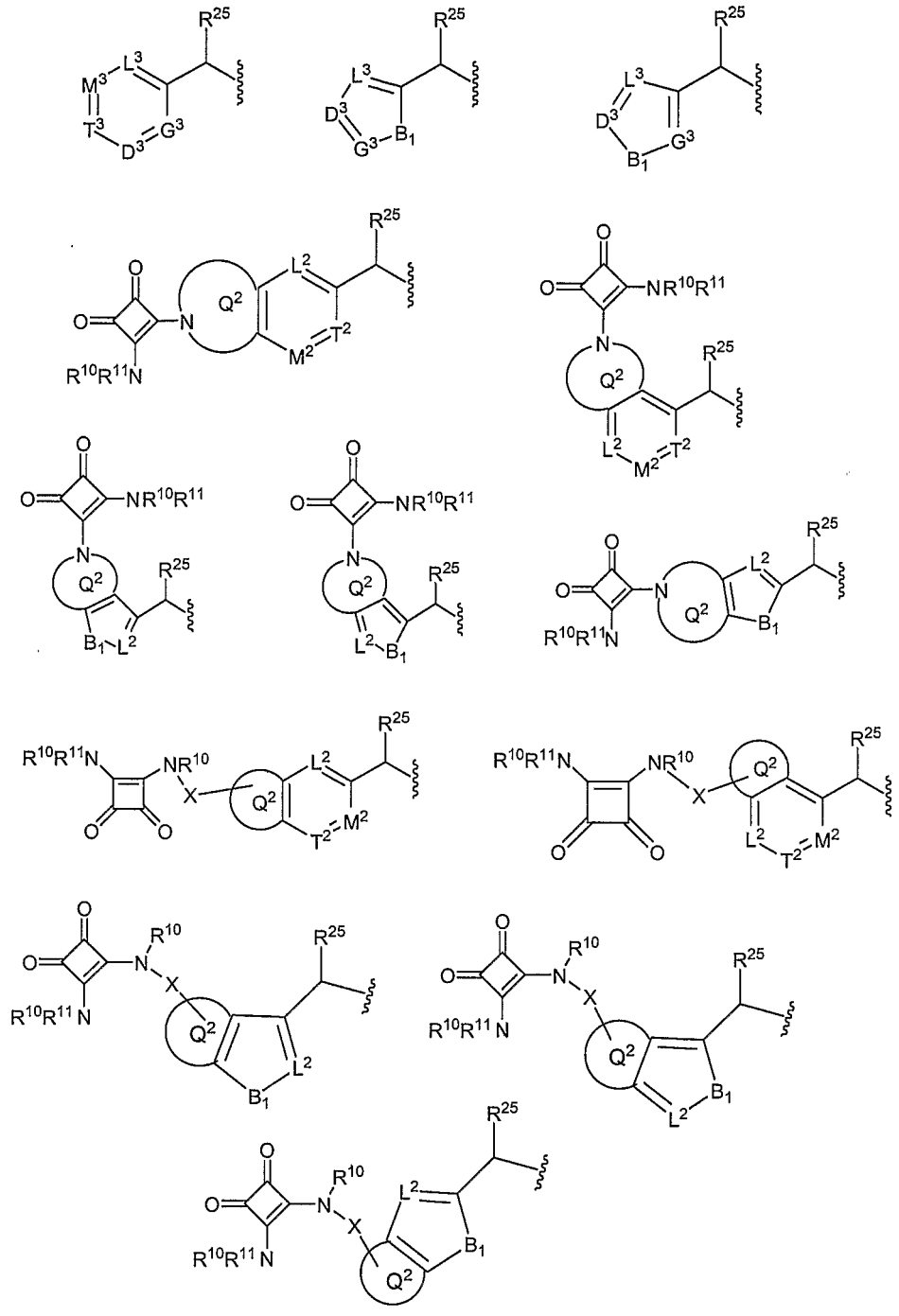
D^2, G^2, L^2, M^2 and T^2 are independently selected from the group consisting of CR^{18} and N.

60. The compound of claim 59, wherein R^1 is selected from the group consisting of:




;

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; and

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61. The compound of claim 48, wherein R^1 is selected from the group consisting of:



wherein:

R^5 is independently selected from the group consisting of hydrogen, alkyl, $C(O)NR^{10}R^{11}$, aryl, arylalkyl, $SO_2NR^{10}R^{11}$ and $C(O)OR^{10}$ wherein alkyl, aryl and arylalkyl are optionally substituted one or more times;

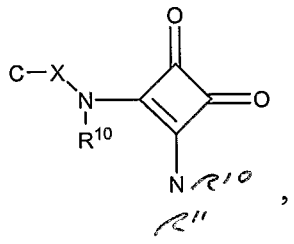
R^{18} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{19} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two R^{19} groups together at one carbon atom form =O, =S or $=NR^{10}$;

R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $CONR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl and haloalkyl are optionally substituted one or more times;

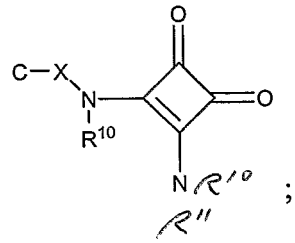
L^2, M^2, and T^2 are independently selected from the group consisting of CR^{18} and N;

L^3, M^3, T^3, D^3, and G^3 are independently selected from N, CR^{18}, and



,

with the provision that one of L^3, M^3, T^3, D^3, and G^3 is

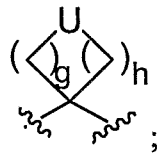


;

B_1 is selected from the group consisting of NR^{10}, O and S;

X is selected from the group consisting of a bond and $(CR^{10}R^{11})_wE(CR^{10}R^{11})_w$

E is selected from the group consisting of a bond, $CR^{10}R^{11}$, O, NR^5, S, S=O, $S(=O)_2$, C(=O), $N(R^{10})(C=O)$, $(C=O)N(R^{10})$, $N(R^{10})S(=O)_2$, $S(=O)_2N(R^{10})$, C=N-OR^{11}, $-C(R^{10}R^{11})C(R^{10}R^{11})-$, $-CH_2-W^1-$ and



;

W^1 is selected from the group consisting of O, NR^5, S, S=O, $S(=O)_2$, $N(R^{10})(C=O)$, $N(R^{10})S(=O)_2$ and $S(=O)_2N(R^{10})$;

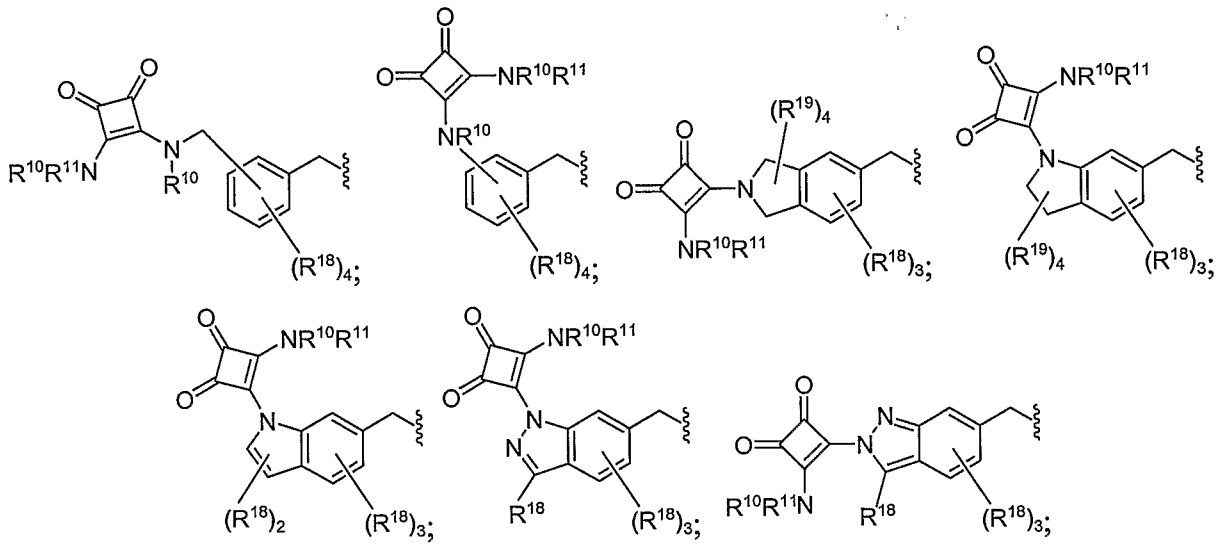
U is selected from $C(R^5R^{10})$, NR^5, O, S, S=O, $S(=O)_2$;

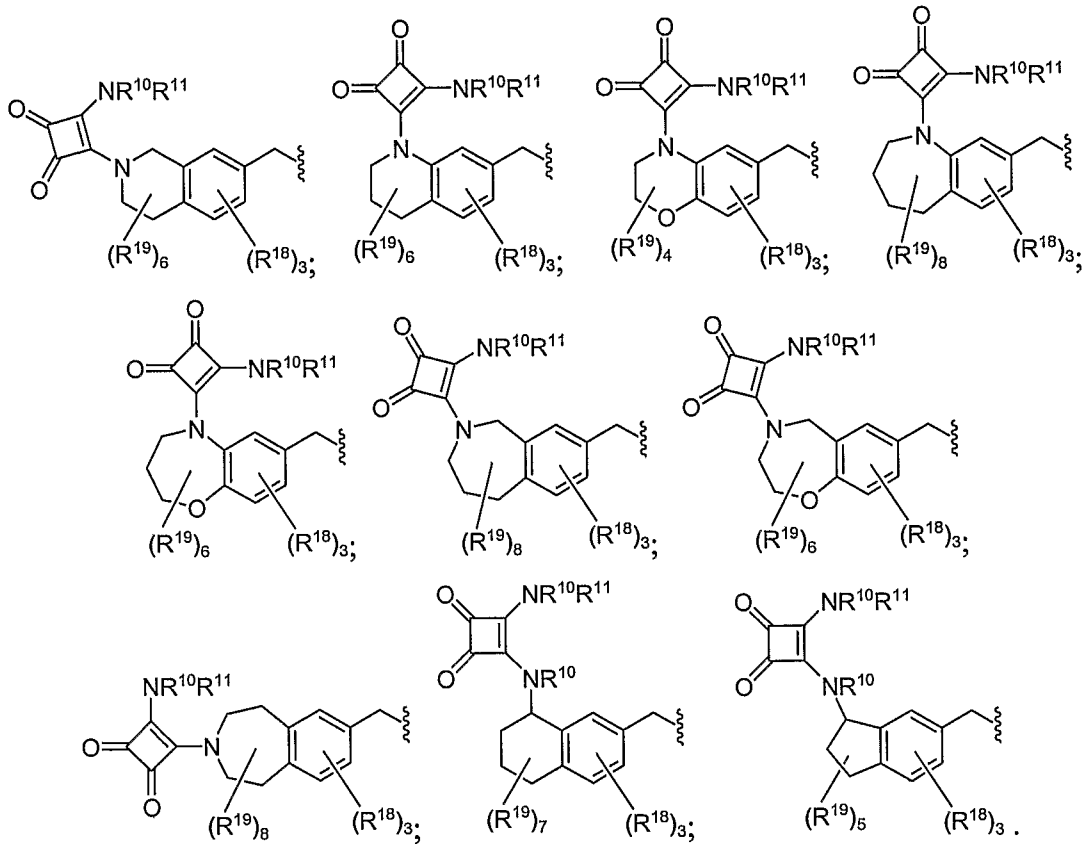
g and h are independently selected from 0-2;

w is selected from 0-4; and

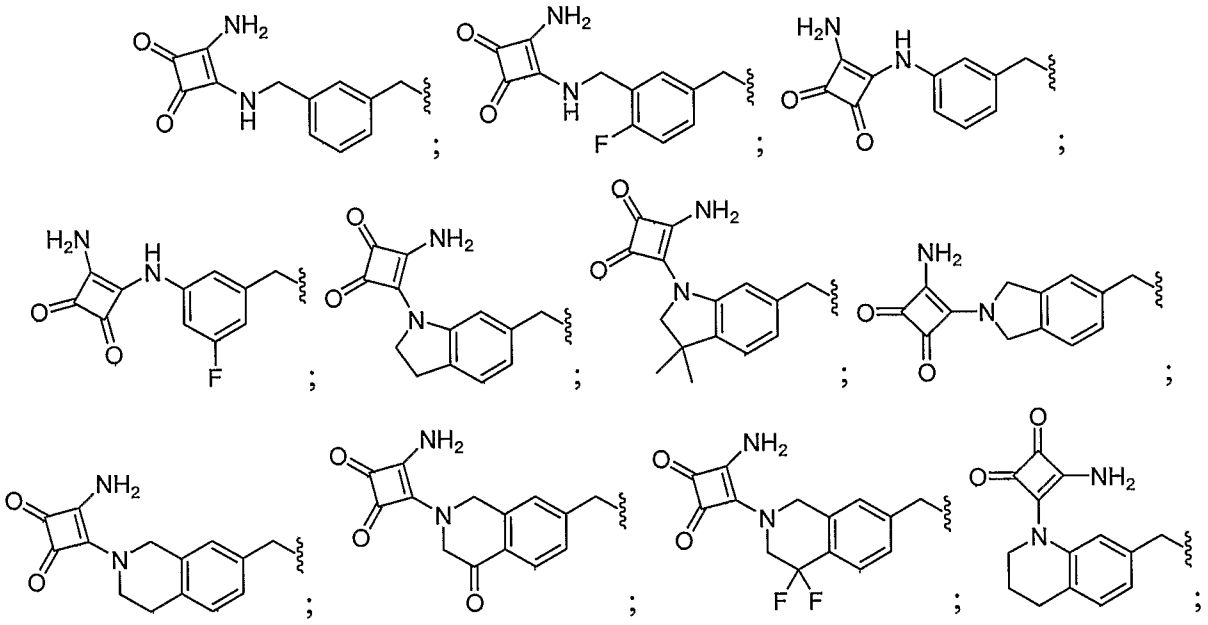
Q^2 is a 5- to 8-membered ring consisting of cycloalkyl, heterocycloalkyl, aryl, heteroaryl, which is optionally substituted one or more times with R^{19}.

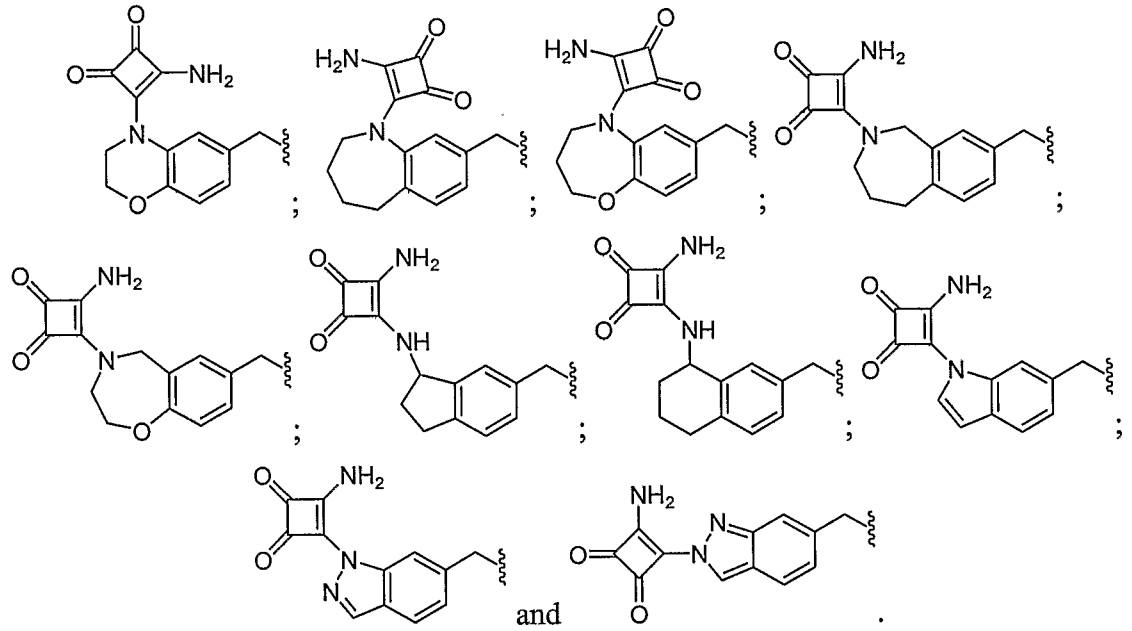
62. The compound of claim 61, wherein R^1 is selected from the group consisting of:



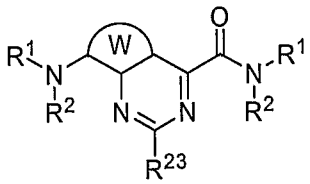


63. The compound of claim 62, wherein R^1 is selected from the group consisting of:





64. A compound having Formula (V):



Formula (V)

wherein:

R^1 in each occurrence is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl,

heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)\text{-}NR^{11}$-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)\text{-}NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{23} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N{=}CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$ are optionally substituted;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted;

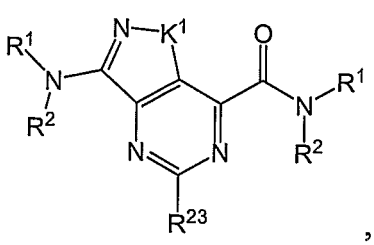
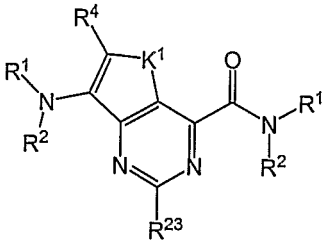
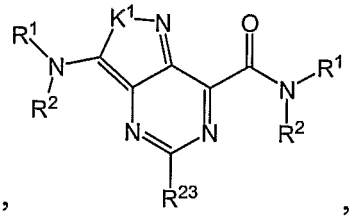
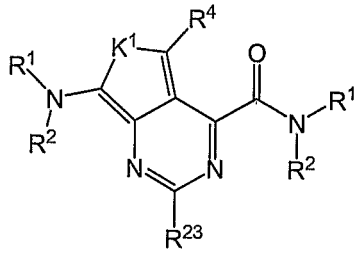
W is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

x is selected from 0 to 2;

y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

65. The compound of claim 64, selected from the group consisting of:

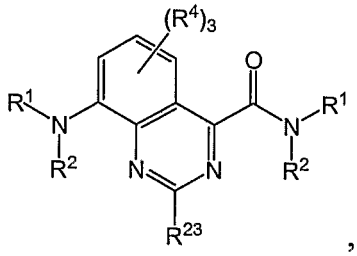
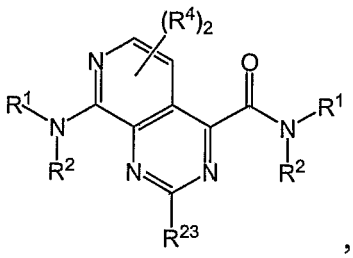
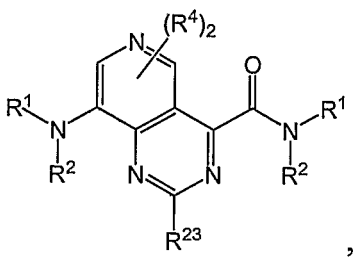
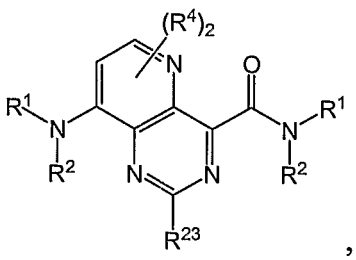
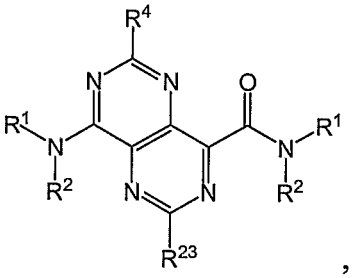
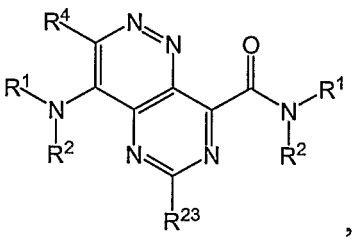
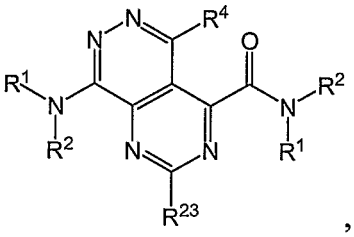
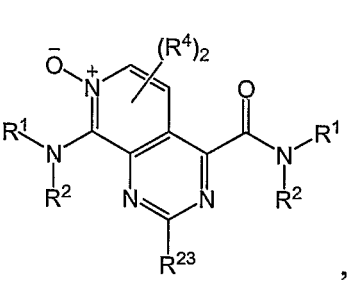
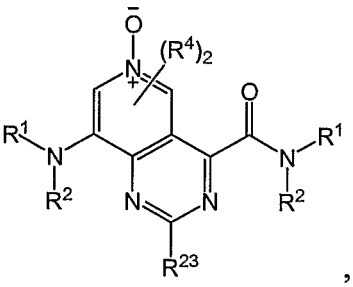
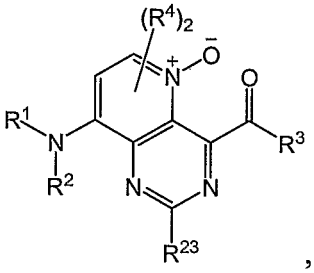
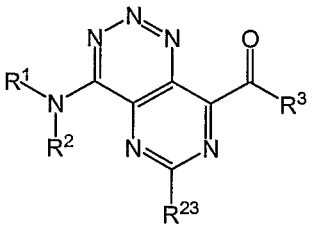

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wherein:

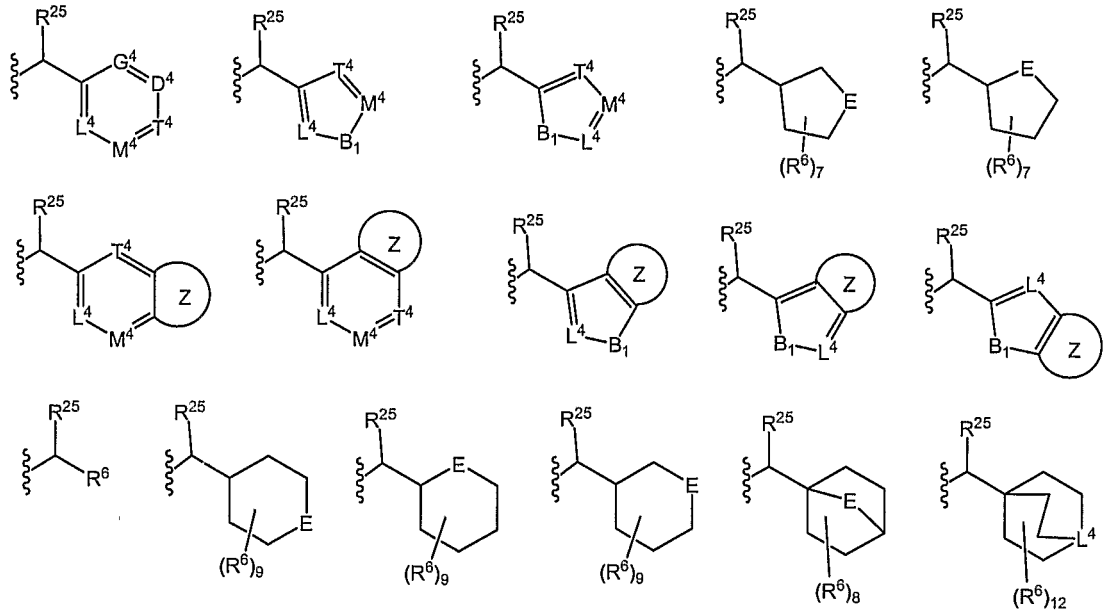
K^1 is O, S, or NR^{51}; and

R^{51} is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and haloalkyl, wherein alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and haloalkyl are optionally substituted one or more times;

66. The compound of formula 64, selected from the group consisting of:


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, and

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67. The compound of claim 64, wherein at least one R^1 is selected from the group consisting of:



wherein:

R^5 is independently selected from the group consisting of hydrogen, alkyl, $C(O)NR^{10}R^{11}$, aryl, arylalkyl, $SO_2NR^{10}R^{11}$ and $C(O)OR^{10}$ wherein alkyl, aryl and arylalkyl are optionally substituted one or more times;

R^6 is selected from the group consisting of R^9, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $C(O)OR^{10}$, $CH(CH_3)CO_2H$, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$P(O)_2OH$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=N\text{-}CN)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=N\text{-}CN)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=N\text{-}NO_2)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=N\text{-}NO_2)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2NR^{10}$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2NR^{10}$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $S(O)_2NR^{10}$-alkyl, $S(O)_2$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $(C_0\text{-}C_6)$-alkyl-C(O)-NR^{11}-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$,

$(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)$-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{11}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^6 group is optionally substituted by one or more R^{14} groups;

R^9 is independently selected from the group consisting of hydrogen, alkyl, halo, CHF_2, CF_3, OR^{10}, $NR^{10}R^{11}$, NO_2, and CN, wherein alkyl is optionally substituted one or more times;

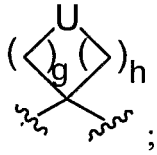
R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $C(O)NR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

R^{30} is selected from the group consisting of alkyl and $(C_0\text{-}C_6)$-alkyl-aryl, wherein alkyl and aryl are optionally substituted;

B_1 is selected from the group consisting of NR^{10}, O and S;

D^4, G^4, L^4, M^4, and T^4, are independently selected from CR^6 or N;

E is selected from the group consisting of a bond, $CR^{10}R^{11}$, O, NR^5, S, S=O, $S(=O)_2$, $C(=O)$, $N(R^{10})(C=O)$, $(C=O)N(R^{10})$, $N(R^{10})S(=O)_2$, $S(=O)_2N(R^{10})$, C=N-OR^{11}, $-C(R^{10}R^{11})C(R^{10}R^{11})-$, $-CH_2-W^1-$ and



;

W^1 is selected from the group consisting of O, NR^5, S, S=O, $S(=O)_2$, $N(R^{10})(C=O)$, $N(R^{10})S(=O)_2$ and $S(=O)_2N(R^{10})$;

U is selected from $C(R^5R^{10})$, NR^5, O, S, S=O, $S(=O)_2$;

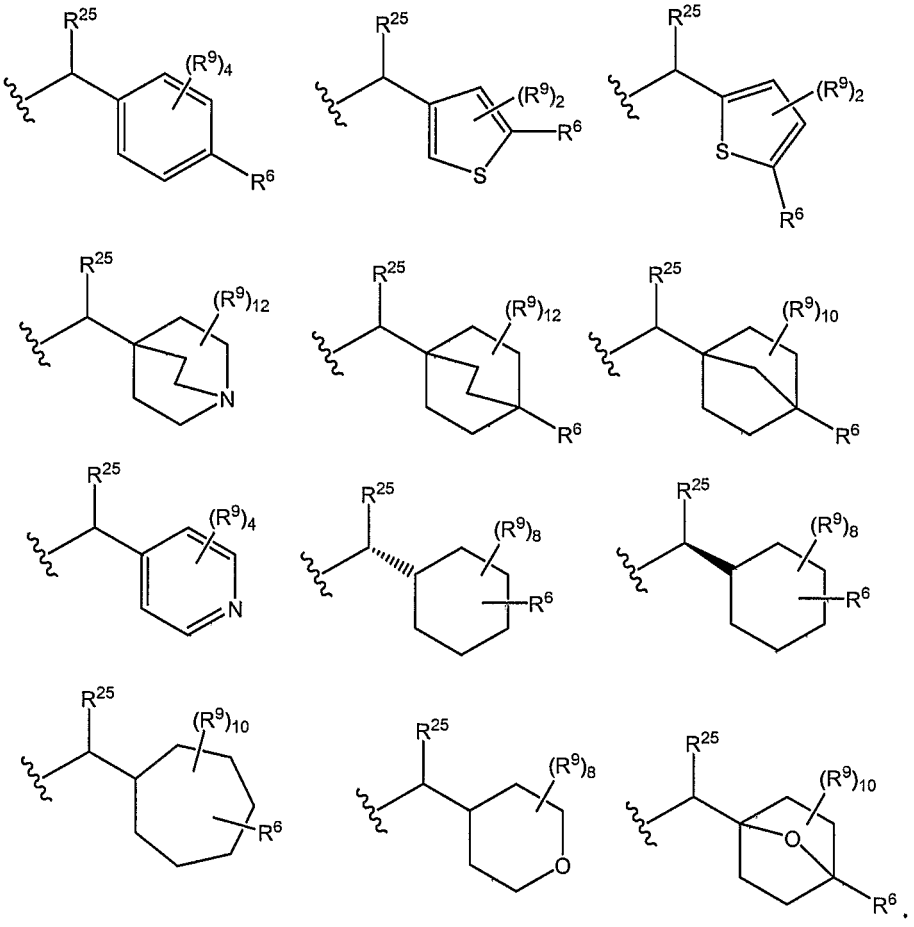
g and h are independently selected from 0-2;

p is selected from 0-6;

y is selected from 1 and 2; and

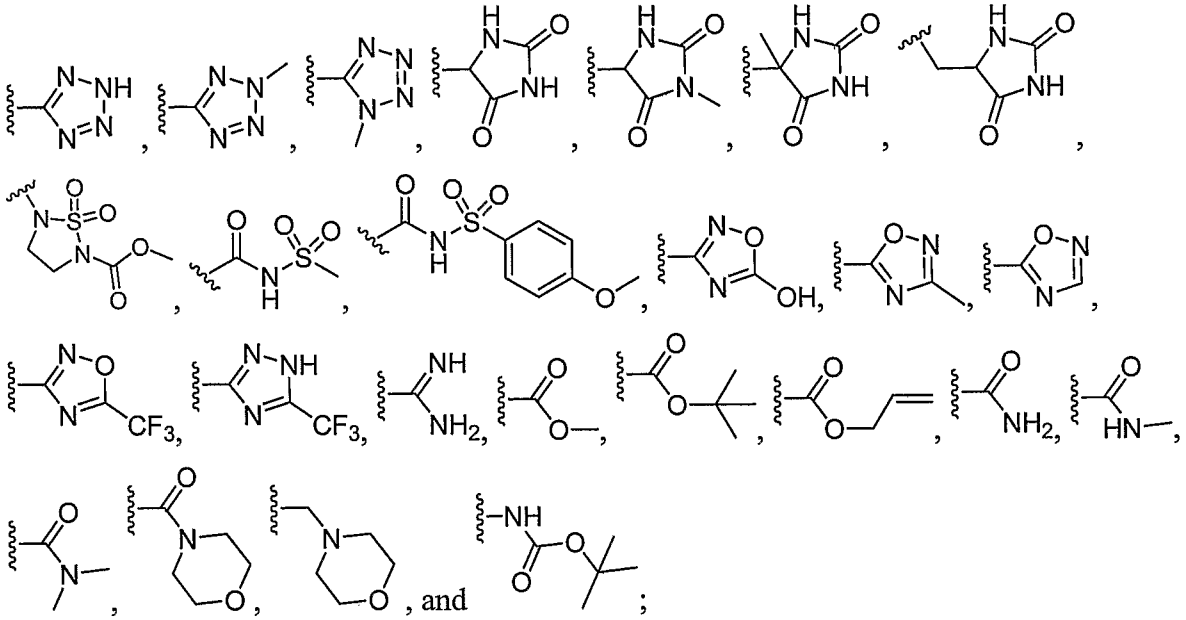
Z is a 5- to 8-membered ring consisting of cycloalkyl, heterocycloalky, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted one ore more times.

68. The compound of claim 67, wherein at least one R^1 is selected from the group consisting of:



69. The compound of claim 68, wherein:

R^6 is selected from the group consisting of hydrogen, halo, CN, OH, CH_2OH, CF_3, CHF_2, OCF_3, $OCHF_2$, $COCH_3$, SO_2CH_3, SO_2CF_3, SO_2NH_2, SO_2NHCH_3, $SO_2N(CH_3)_2$, NH_2, $NHCOCH_3$, $N(COCH_3)_2$, $NHCONH_2$, $NHSO_2CH_3$, alkoxy, alkyl, CO_2H,

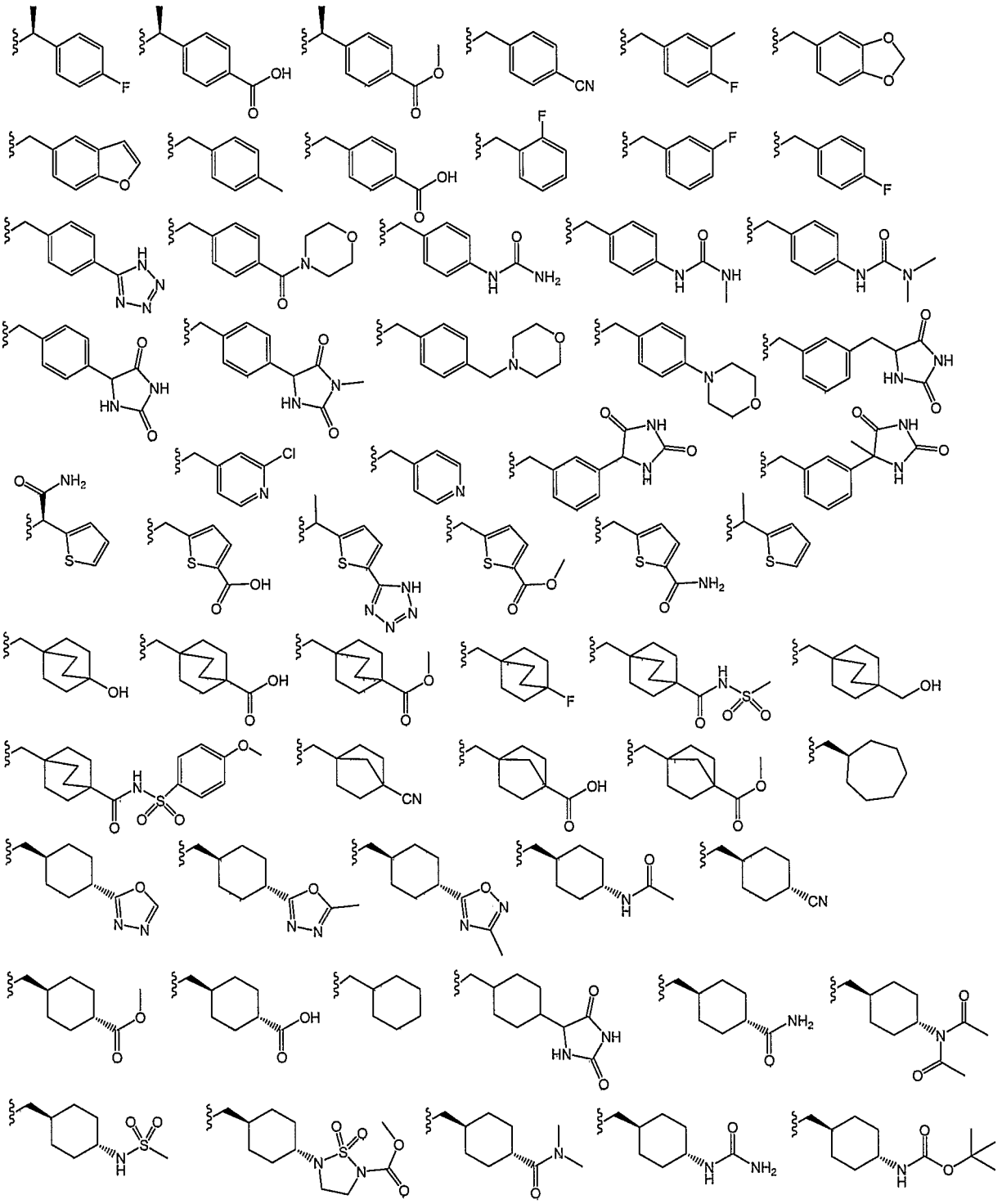


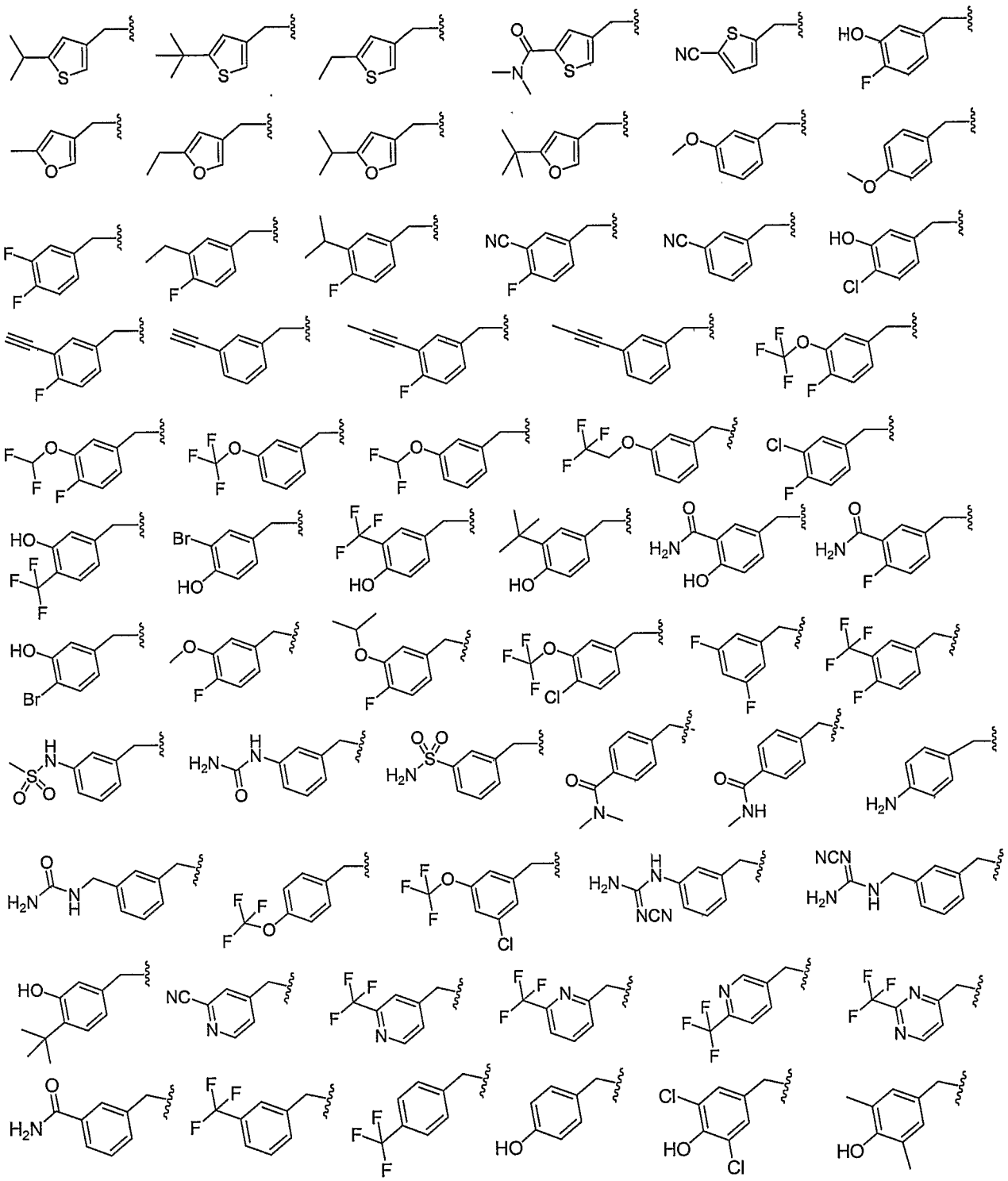
wherein

R^9 is independently selected from the group consisting of hydrogen, fluoro, chloro, CH_3, CF_3, CHF_2, OCF_3, and $OCHF_2$;

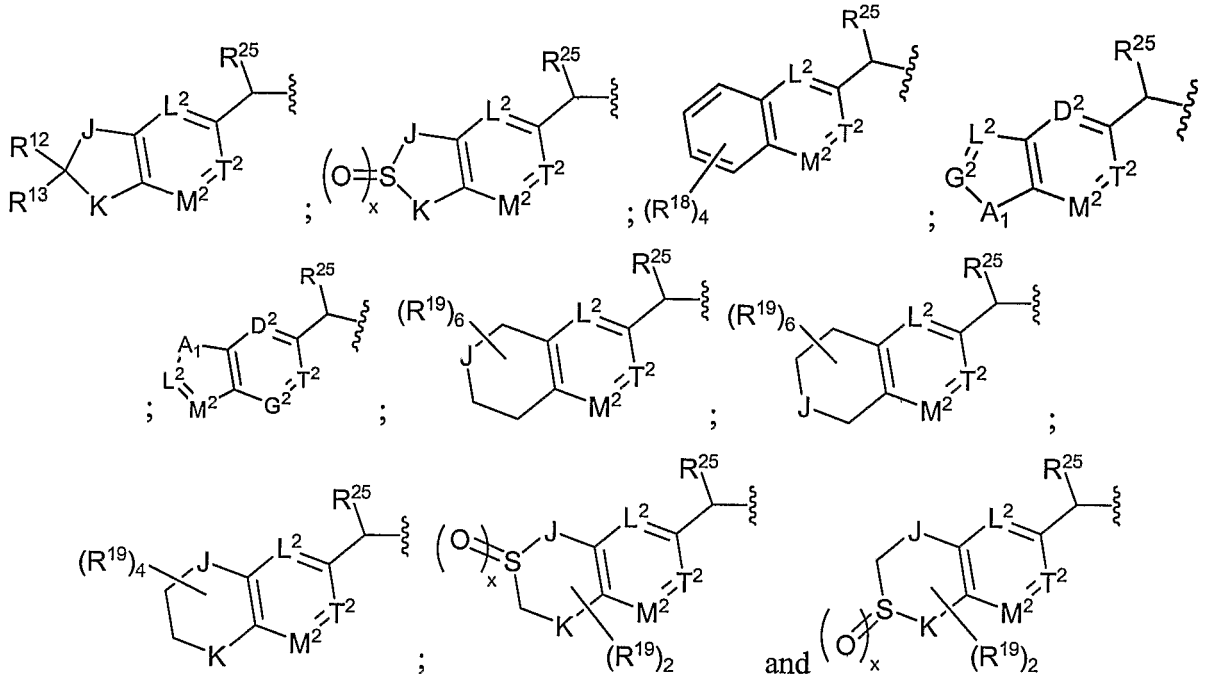
R^{25} is selected from the group consisting of hydrogen, CH_3, COOMe, COOH, and $CONH_2$.

70. The compound of claim 64, wherein at least one R^1 is selected from the group consisting of:





71. The compound of claim 64, wherein at least one R^1 is selected from the group consisting of:



wherein:

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, alkyl and halo, wherein alkyl is optionally substituted one or more times, or optionally R^{12} and R^{13} together form =O, =S or $=NR^{10}$;

R^{18} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{19} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two R^{19} groups together at one carbon atom form =O, =S or $=NR^{10}$;

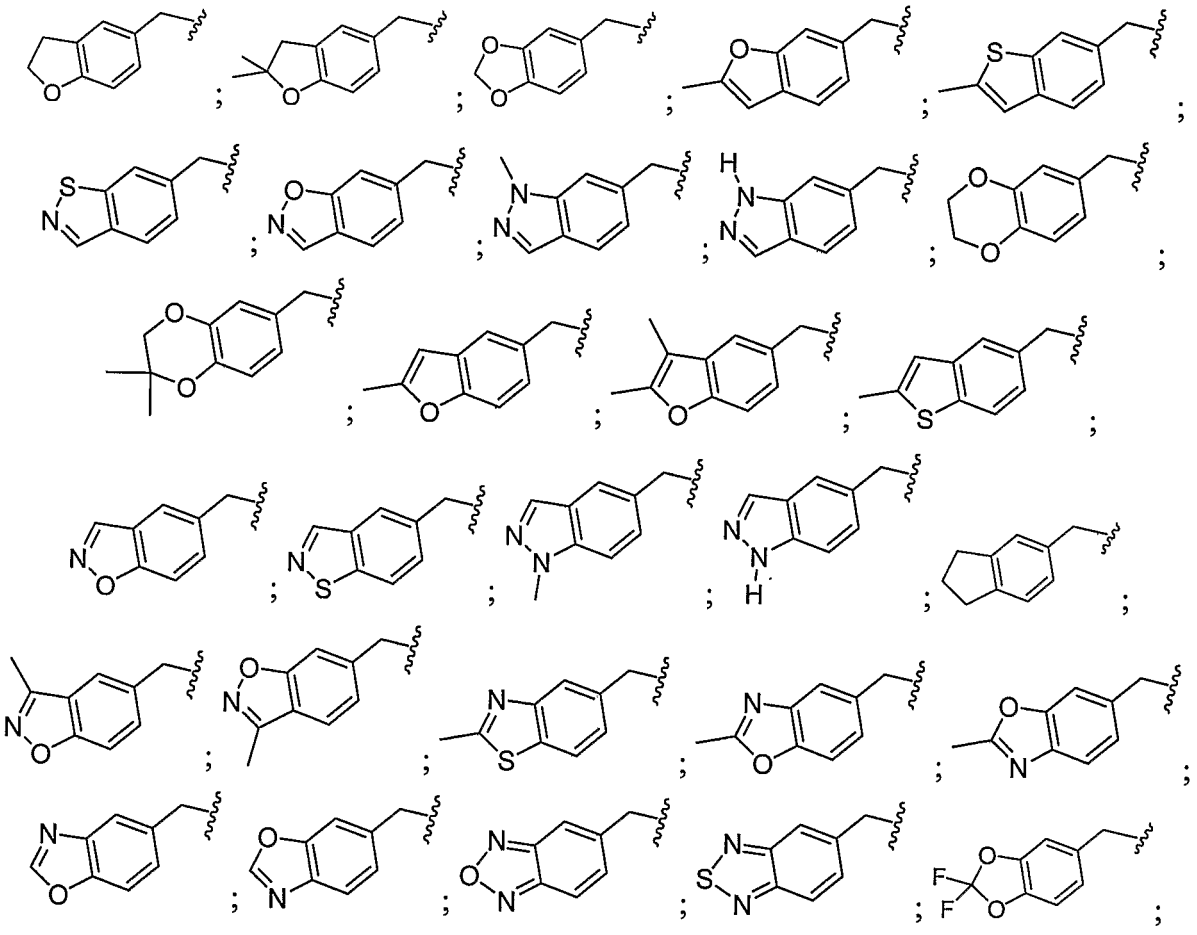
R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $C(O)NR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

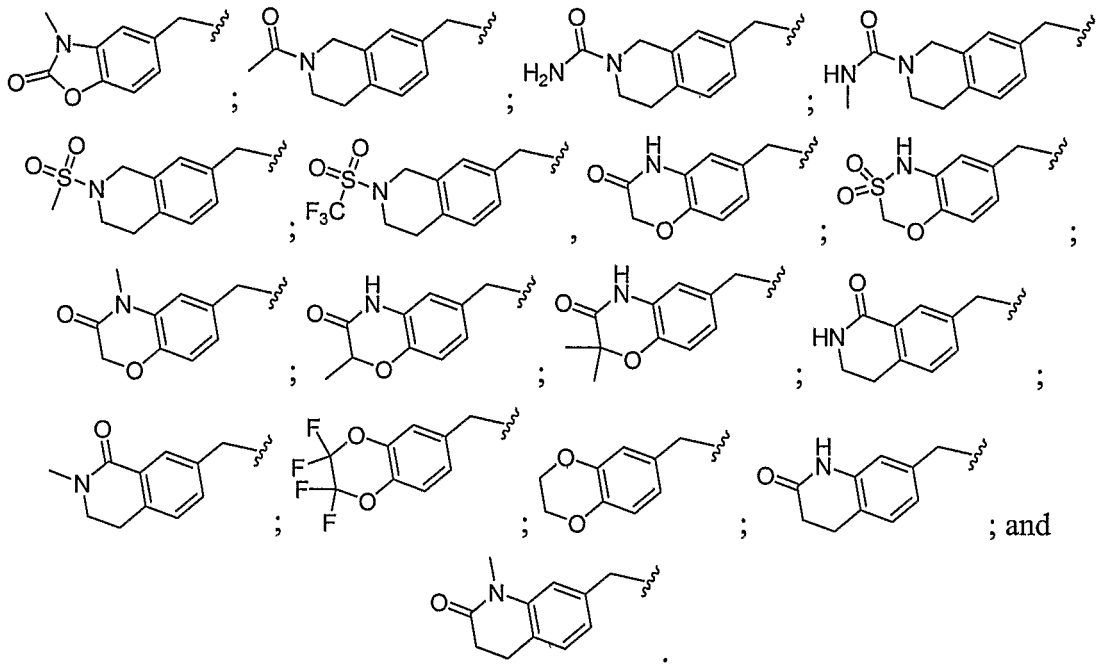
J and K are independently selected from the group consisting of $CR^{10}R^{18}$, NR^{10}, O and $S(O)_x$;

A_1 is selected from the group consisting of NR^{10}, O and S;

D^2, G^2, L^2, M^2 and T^2 are independently selected from the group consisting of CR^{18} and N.

72. The compound of claim 71, wherein at least one R^1 is selected from the group consisting of:

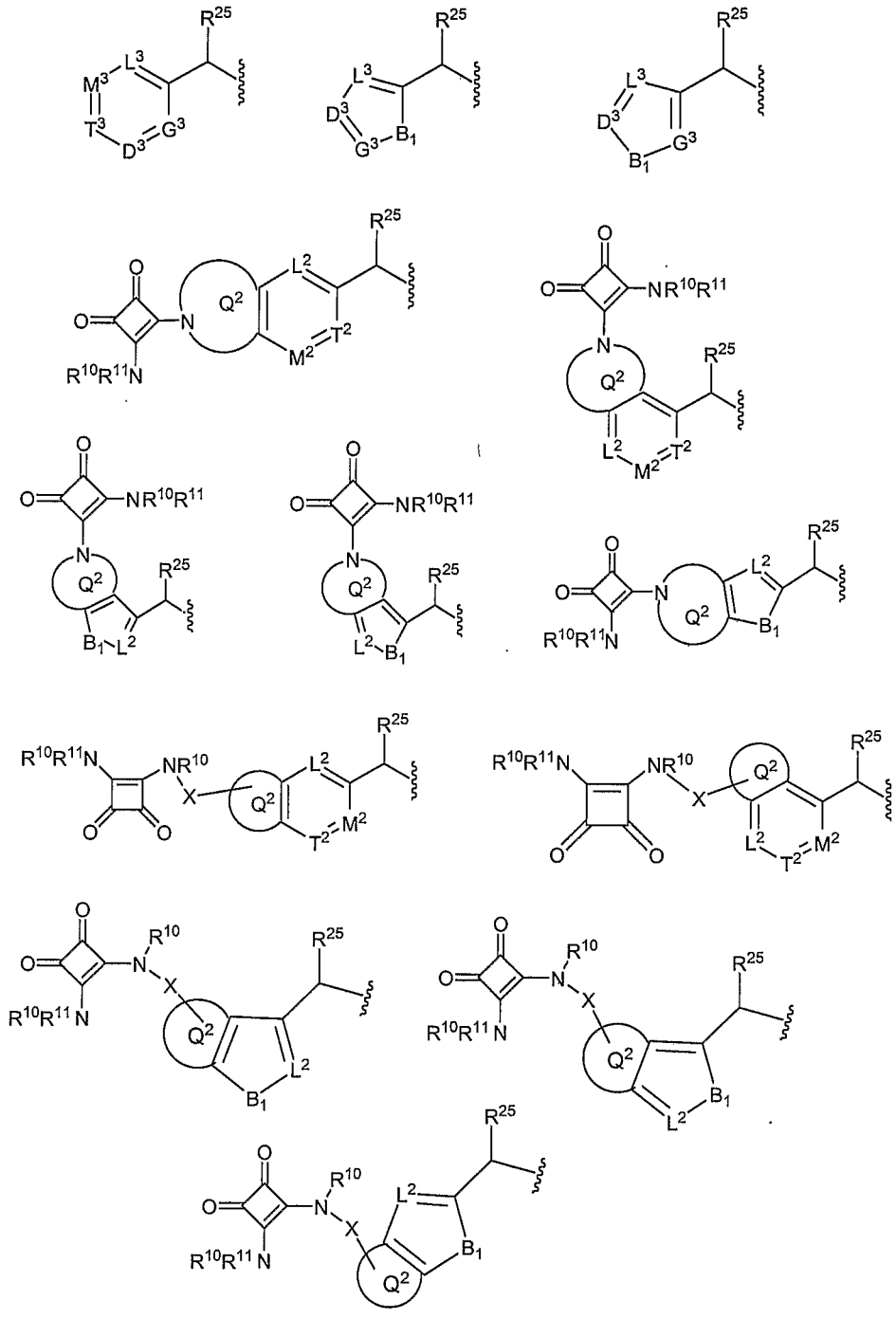




; and

.

73. The compound of claim 64, wherein one R^1 is selected from the group consisting of:



wherein:

R^5 is independently selected from the group consisting of hydrogen, alkyl, $C(O)NR^{10}R^{11}$, aryl, arylalkyl, $SO_2NR^{10}R^{11}$ and $C(O)OR^{10}$ wherein alkyl, aryl and arylalkyl are optionally substituted one or more times;

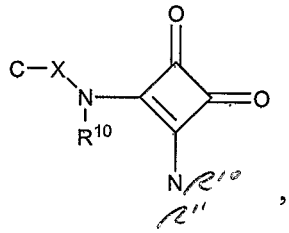
R^{18} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{19} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two R^{19} groups together at one carbon atom form =O, =S or $=NR^{10}$;

R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $CONR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl and haloalkyl are optionally substituted one or more times;

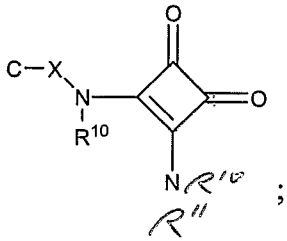
L^2, M^2, and T^2 are independently selected from the group consisting of CR^{18} and N;

L^3, M^3, T^3, D^3, and G^3 are independently selected from N, CR^{18}, and



,

with the provision that one of L^3, M^3, T^3, D^3, and G^3 is

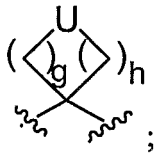


;

B_1 is selected from the group consisting of NR^{10}, O and S;

X is selected from the group consisting of a bond and $(CR^{10}R^{11})_wE(CR^{10}R^{11})_w$

E is selected from the group consisting of a bond, $CR^{10}R^{11}$, O, NR^5, S, S=O, $S(=O)_2$, C(=O), $N(R^{10})(C=O)$, $(C=O)N(R^{10})$, $N(R^{10})S(=O)_2$, $S(=O)_2N(R^{10})$, C=N-OR^{11}, $-C(R^{10}R^{11})C(R^{10}R^{11})-$, $-CH_2-W^1-$ and



;

W^1 is selected from the group consisting of O, NR^5, S, S=O, $S(=O)_2$, $N(R^{10})(C=O)$, $N(R^{10})S(=O)_2$ and $S(=O)_2N(R^{10})$;

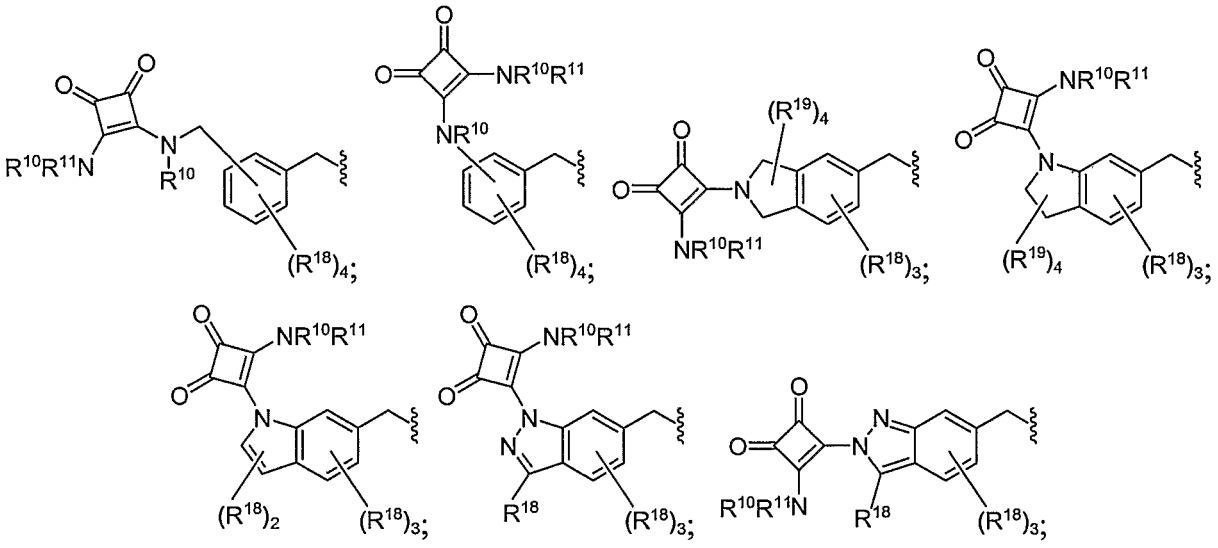
U is selected from $C(R^5R^{10})$, NR^5, O, S, S=O, $S(=O)_2$;

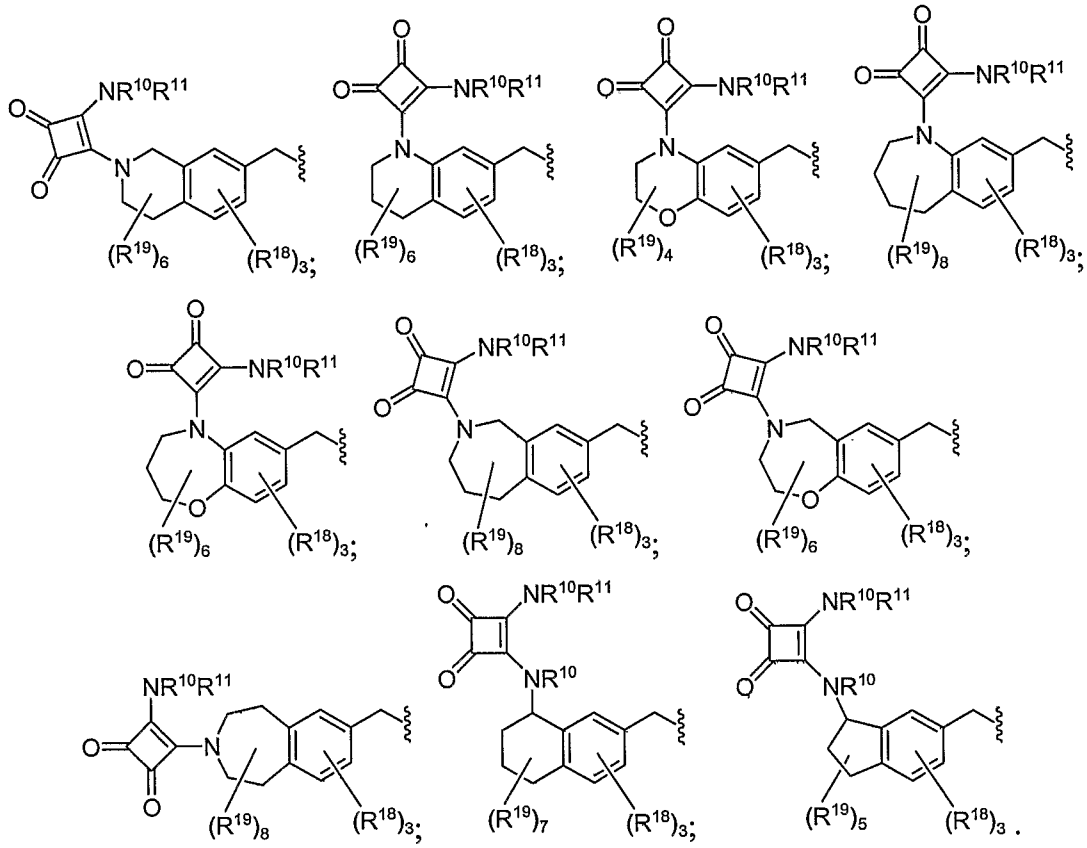
g and h are independently selected from 0-2;

w is selected from 0-4; and

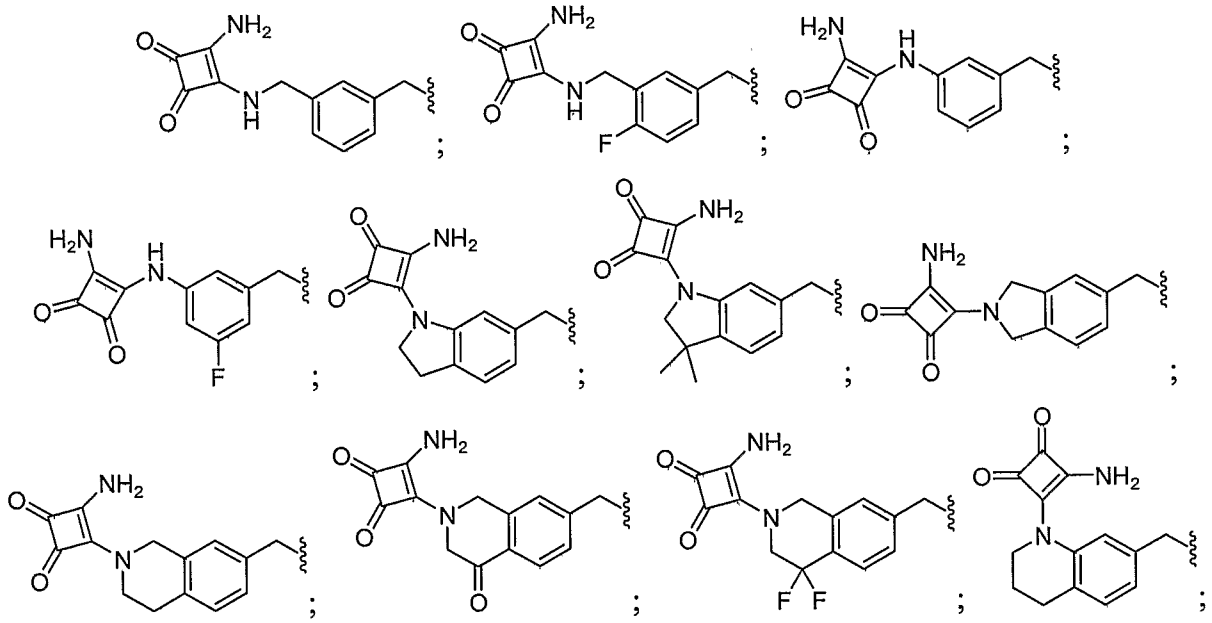
Q^2 is a 5- to 8-membered ring consisting of cycloalkyl, heterocycloalkyl, aryl, heteroaryl, which is optionally substituted one or more times with R^{19}.

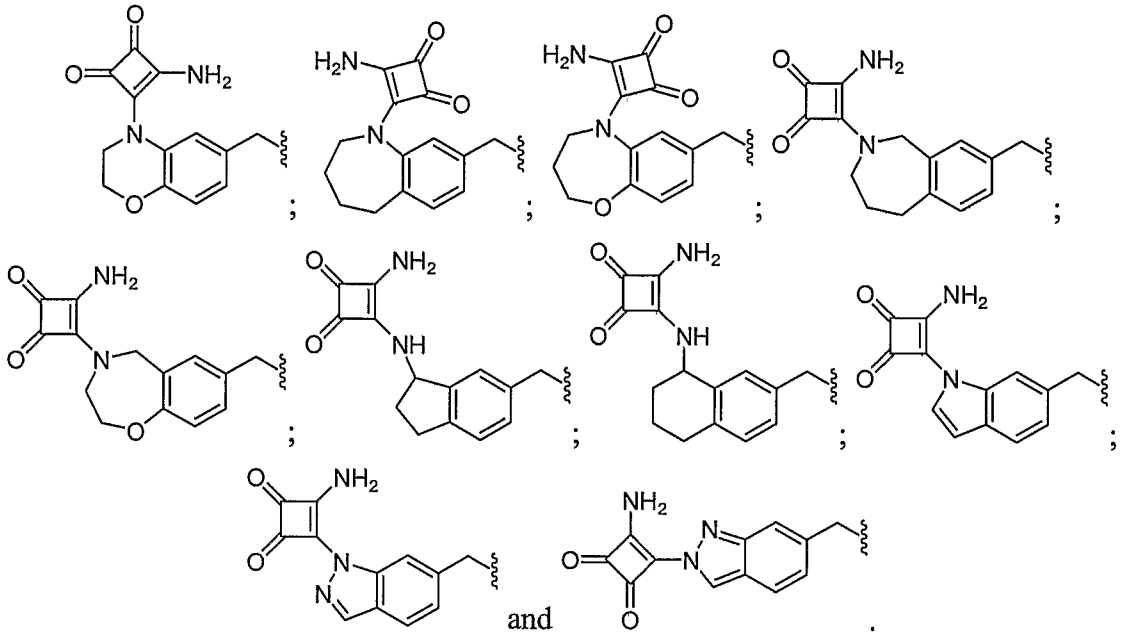
74. The compound of claim 73, wherein one R^1 is selected from the group consisting of:



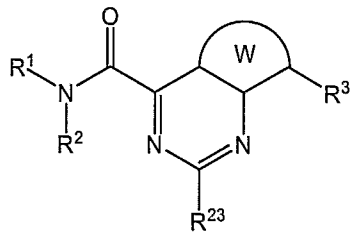


75. The compound of claim 73, wherein one R^1 is selected from the group consisting of:





76. A compound having Formula (VI):



Formula (VI)

wherein:

R^1 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused

heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^3 is $NR^{20}R^{21}$;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-C(O)-NR^{11}-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and

optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{20} is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted;

R^{21} is a bicyclic or tricyclic fused ring system, wherein at least one ring is partially saturated, and wherein the bicyclic or tricyclic fused ring system is optionally substituted;

R^{23} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N{=}CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$ are optionally substituted;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted;

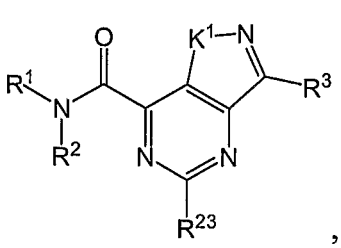
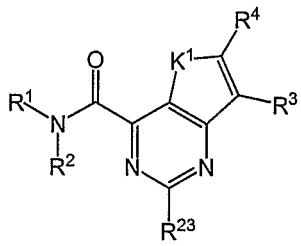
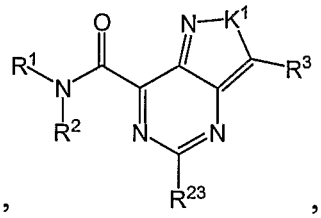
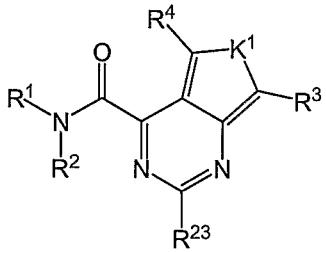
W is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

x is selected from 0 to 2;

y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

77. The compound of claim 76, selected from the group consisting of:

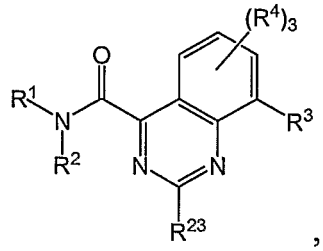
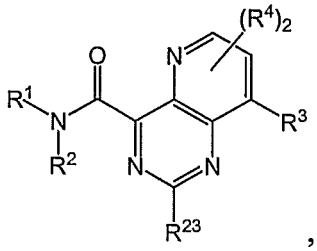
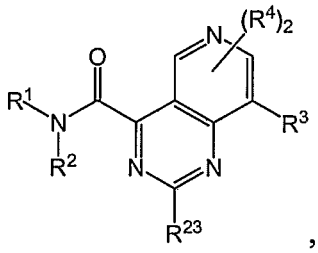
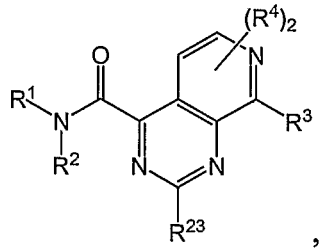
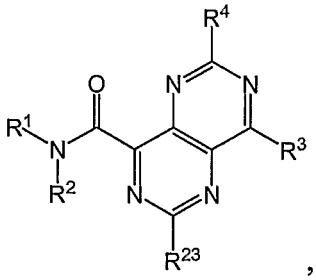
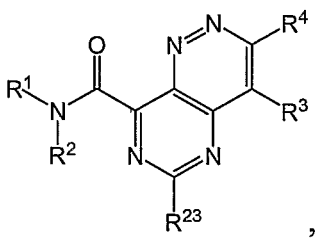
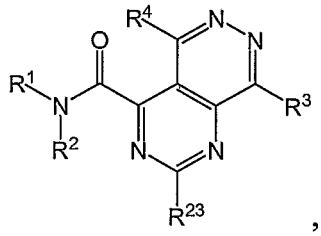
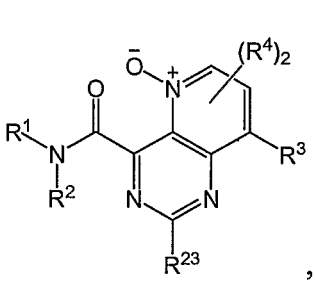
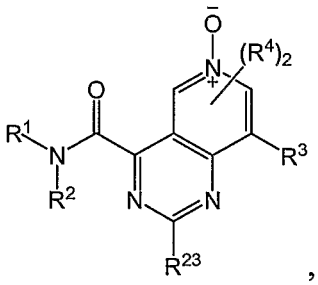
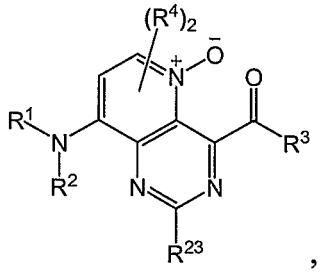
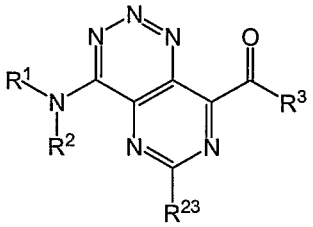

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, and


wherein:

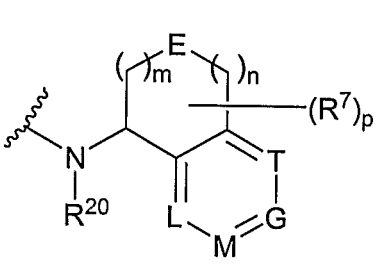
K^1 is O, S, or NR^{51}; and

R^{51} is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and haloalkyl, wherein alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and haloalkyl are optionally substituted one or more times.

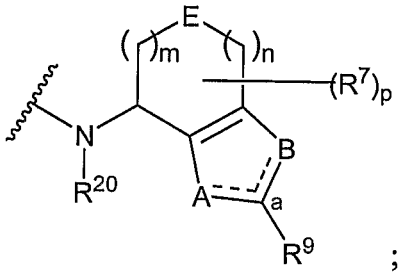
78. The compound of claim 76, selected from the group consisting of:


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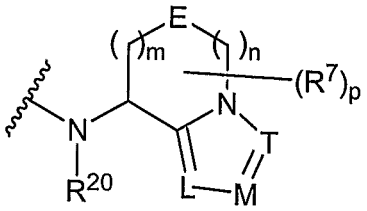
79. The compound of claim 76, wherein R^3 is selected from the group consisting of:



;



; and



wherein:

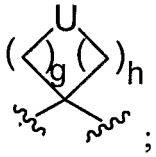
R^5 is independently selected from the group consisting of hydrogen, alkyl, $C(O)NR^{10}R^{11}$, aryl, arylalkyl, $SO_2NR^{10}R^{11}$ and $C(O)OR^{10}$ wherein alkyl, aryl and arylalkyl are optionally substituted one or more times;

R^7 is independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, halo, R^4 and $NR^{10}R^{11}$, wherein alkyl and cycloalkyl are optionally substituted one or more times, or optionally two R^7 groups together at the same carbon atom form =O, =S or $=NR^{10}$;

R^9 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, CHF_2, CF_3, OR^{10}, $COOR^{10}$, $CH(CH_3)CO_2H$, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$P(O)_2OH$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=N\text{-}CN)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=N\text{-}CN)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=N\text{-}NO_2)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=N\text{-}NO_2)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2NR^{10}$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2NR^{10}$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $S(O)_2NR^{10}$-alkyl, $S(O)_2$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $(C_0\text{-}C_6)$-alkyl-$C(O)\text{-}NR^{11}$-CN, O-$(C_0\text{-}C_6)$-

alkyl-C(O)$NR^{10}R^{11}$, $S(O)_x$-(C_0-C_6)-alkyl-C(O)OR^{10}, $S(O)_x$-(C_0-C_6)-alkyl-C(O)$NR^{10}R^{11}$, (C_0-C_6)-alkyl-C(O)NR^{10}-(C_0-C_6)-alkyl-$NR^{10}R^{11}$, (C_0-C_6)-alkyl-NR^{10}-C(O)R^{10}, (C_0-C_6)-alkyl-NR^{10}-C(O)OR^{10}, (C_0-C_6)-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, (C_0-C_6)-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, (C_0-C_6)-alkyl-NR^{10}-$S(O)_yR^{11}$, O-(C_0-C_6)-alkyl-aryl and O-(C_0-C_6)-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

E is selected from the group consisting of a bond, $CR^{10}R^{11}$, O, NR^5, S, S=O, $S(=O)_2$, C(=O), $N(R^{10})$(C=O), (C=O)$N(R^{10})$, $N(R^{10})S(=O)_2$, $S(=O)_2N(R^{10})$, C=N-OR^{11}, -$C(R^{10}R^{11})C(R^{10}R^{11})$-, -$CH_2$-$W^1$- and



;

W^1 is selected from the group consisting of O, NR^5, S, S=O, $S(=O)_2$, $N(R^{10})$(C=O), $N(R^{10})S(=O)_2$ and $S(=O)_2N(R^{10})$;

U is selected from the group consisting of $C(R^5R^{10})$, NR^5, O, S, S=O and $S(=O)_2$;

A and B are independently selected from the group consisting of CR^9, CR^9R^{10}, NR^{10}, N, O and S;

G, L, M and T are independently selected from the group consisting of CR^9 and N;

g and h are independently selected from 0-2;

m and n are independently selected from 0-3, provided that:

(1) when E is present, m and n are not both 3;

(2) when E is -CH_2-W^1-, m and n are not 3; and

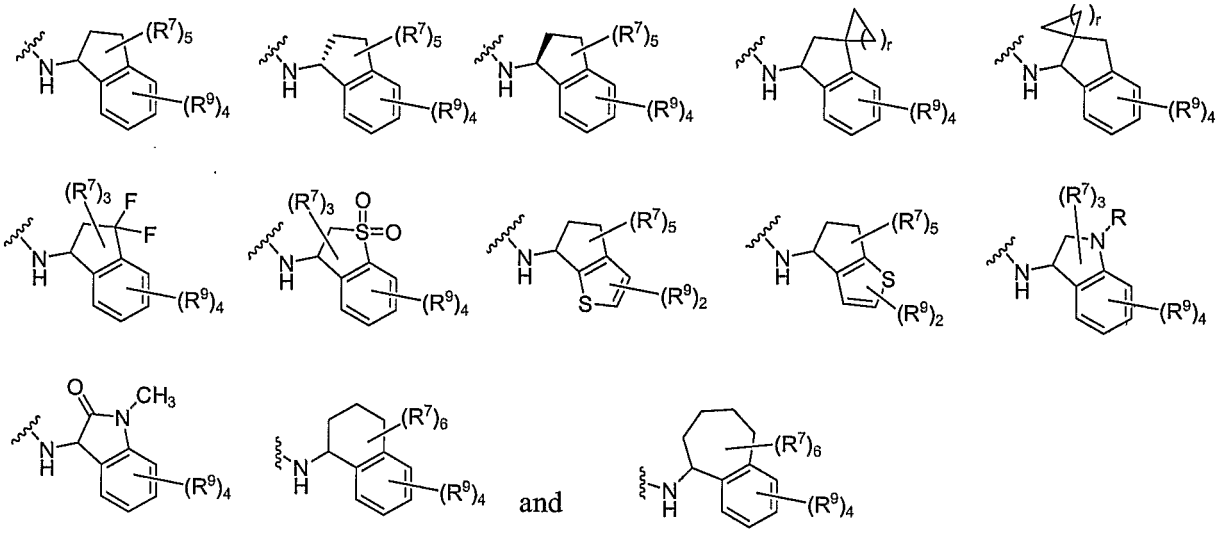
(3) when E is a bond, m and n are not 0;

p is selected from 0-6;

y is selected from 1 and 2; and

wherein the dotted line represents a double bond between one of: carbon "a" and A, or carbon "a" and B.

80. The compound of claim 79, wherein R^3 is selected from the group consisting of:

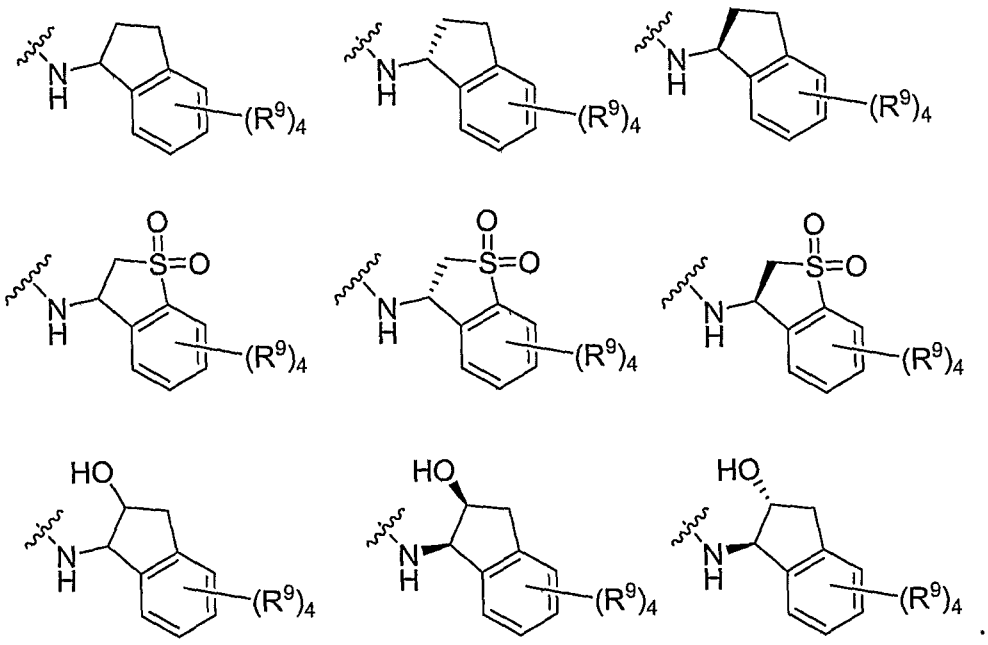


wherein:

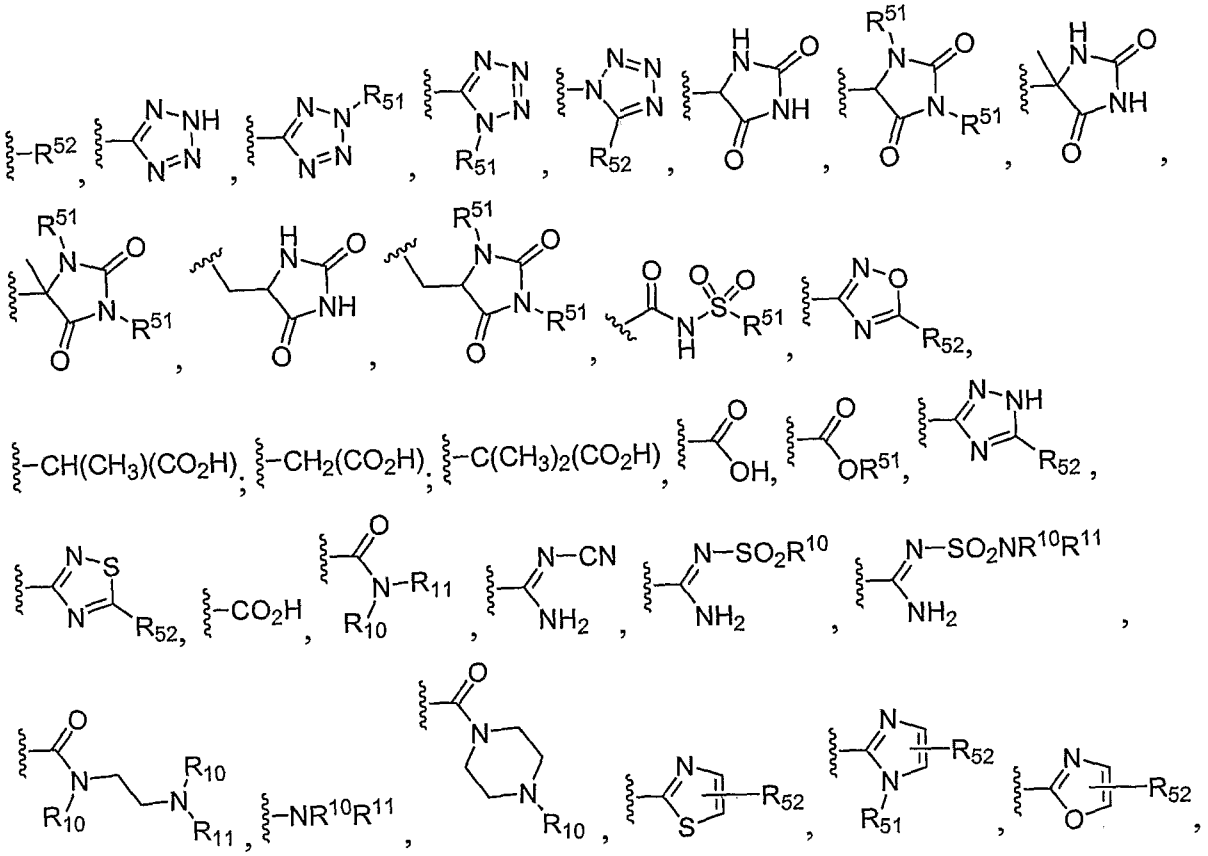
R is selected from the group consisting of $C(O)NR^{10}R^{11}$, COR^{10}, $SO_2NR^{10}R^{11}$, SO_2R^{10}, $CONHCH_3$ and $CON(CH_3)_2$, wherein $C(O)NR^{10}R^{11}$, COR^{10}, $SO_2NR^{10}R^{11}$, SO_2R^{10}, $CONHCH_3$ and $CON(CH_3)_2$ are optionally substituted one or more times; and

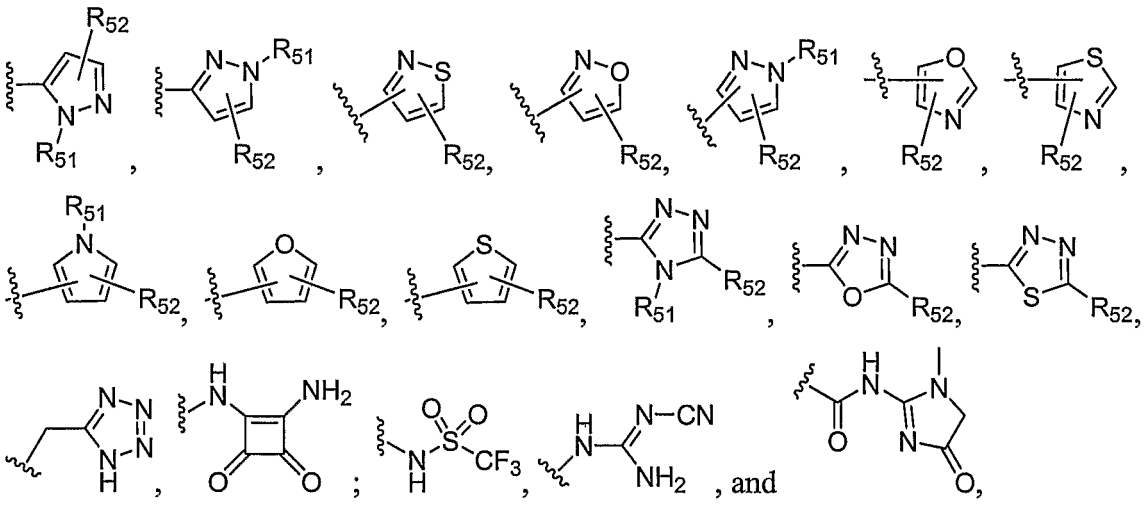
r is selected from 1-4.

81. The compound of claim 79, wherein R^3 is selected from the group consisting of:



82. The compound of claim 81, wherein R^9 is selected from the group consisting of:



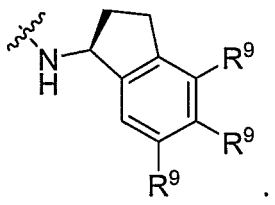


wherein:

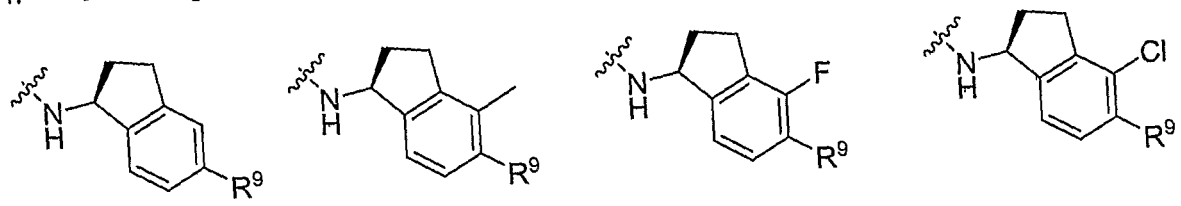
R^{51} is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and haloalkyl, wherein alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and haloalkyl are optionally substituted one or more times; and

R^{52} is selected from the group consisting of hydrogen, halo, CN, hydroxy, alkoxy, fluoroalkoxy, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, haloalkyl, $C(O)NR^{10}R^{11}$ and $SO_2NR^{10}R^{11}$, wherein alkoxy, fluoroalkoxy, alkyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, and haloalkyl are optionally substituted one or more times.

83. The compound of claim 81, wherein R^3 is:

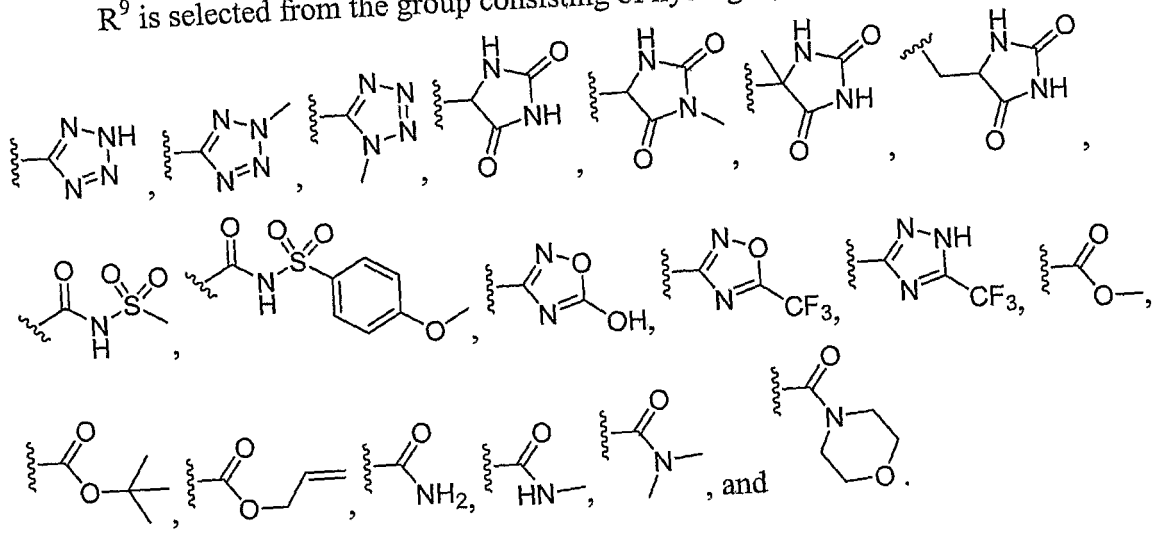


84. The compound of claim 83, wherein R^3 is selected from the group consisting of:

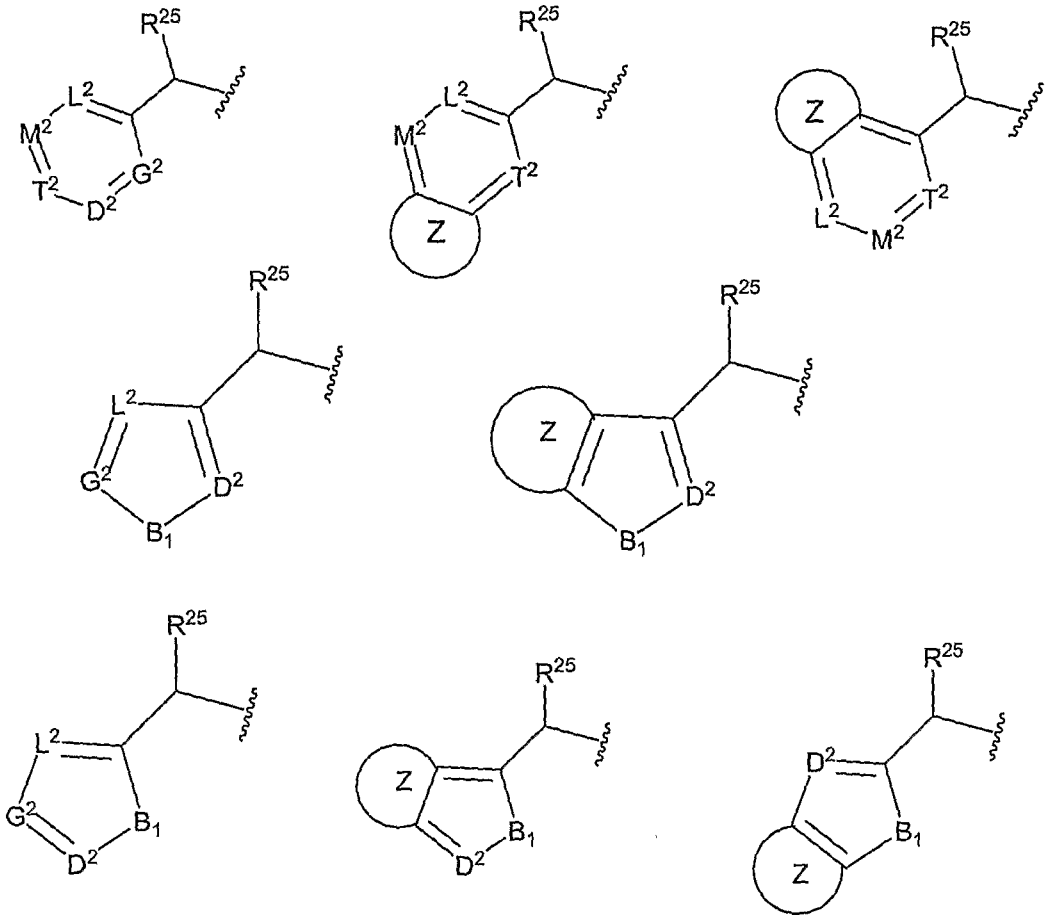


wherein:

R^9 is selected from the group consisting of hydrogen, fluoro, halo, CN, alkyl, CO_2H,



85. The compound of claim 76, wherein R^1 is selected from the group consisting of:



wherein:

R^{18} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl are optionally substituted one or more times;

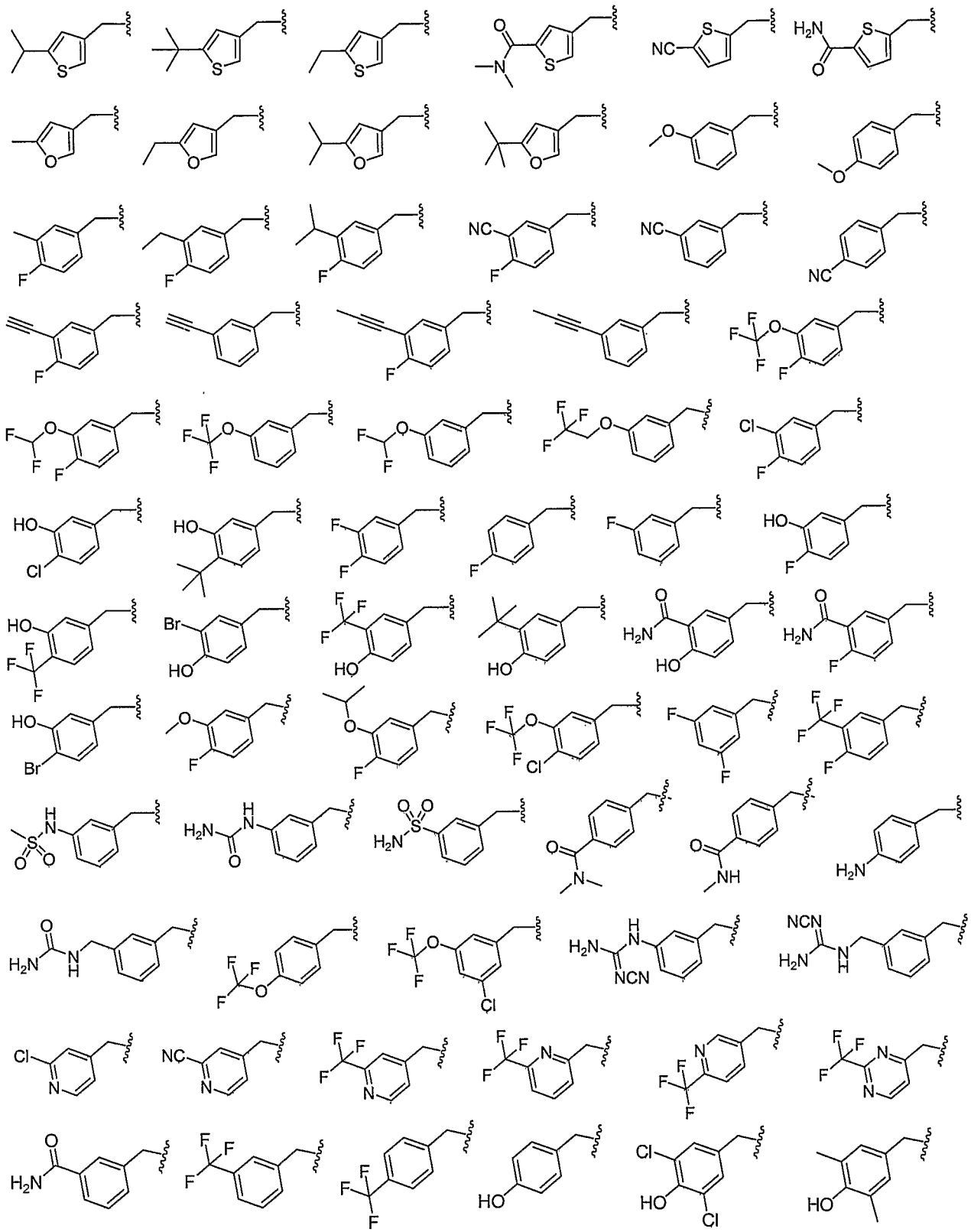
R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $C(O)NR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

B_1 is selected from the group consisting of NR^{10}, O and S;

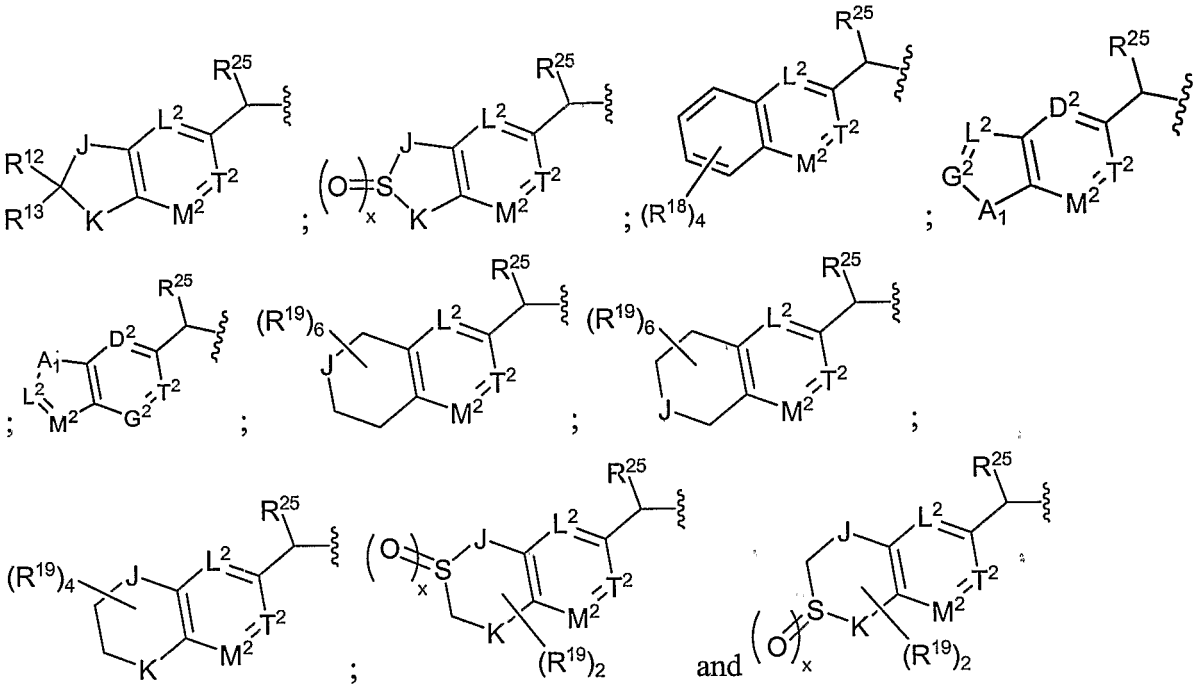
D^2, G^2, L^2, M^2 and T^2 are independently selected from the group consisting of CR^{18} and N; and

Z is a 5- to 8-membered ring selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted one or more times.

86. The compound of claim 85, wherein R^1 is selected from the group consisting of:



87. The compound of claim 76, wherein R^1 is selected from the group consisting of:



wherein:

R^{12} and R^{13} are independently selected from the group consisting of hydrogen, alkyl and halo, wherein alkyl is optionally substituted one or more times, or optionally R^{12} and R^{13} together form =O, =S or $=NR^{10}$;

R^{18} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{19} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two R^{19} groups together at one carbon atom form =O, =S or $=NR^{10}$;

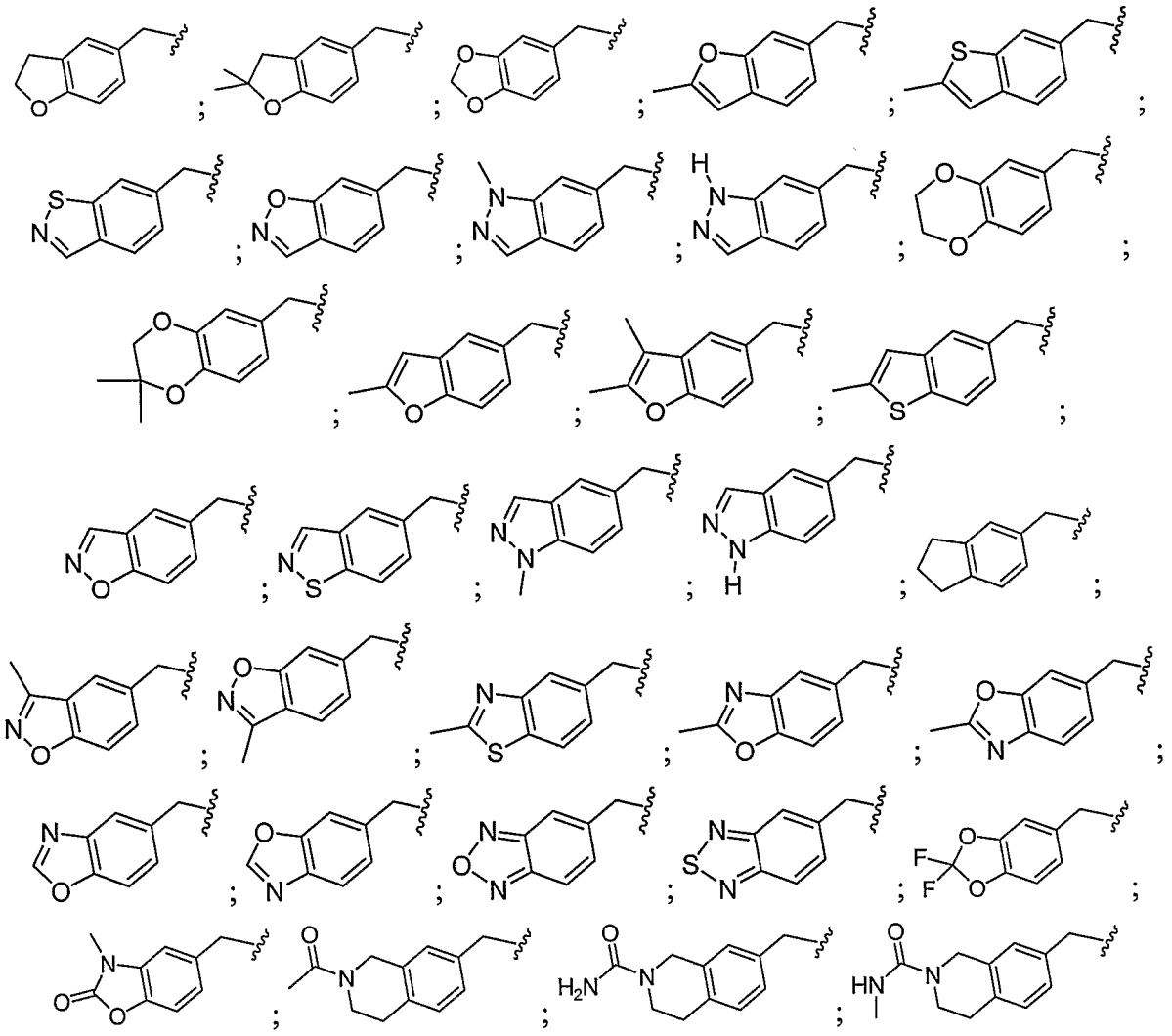
R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $C(O)NR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

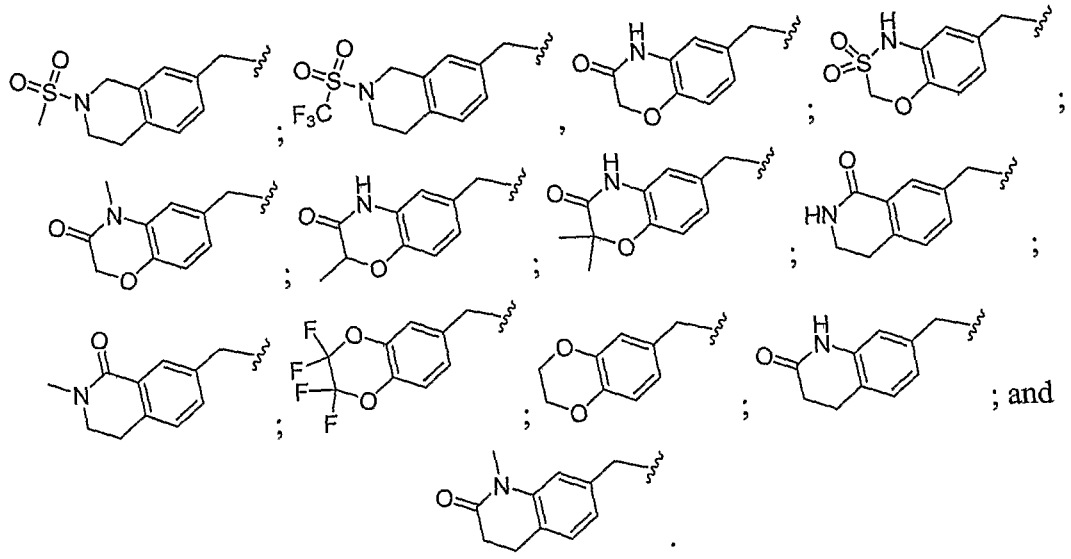
J and K are independently selected from the group consisting of $CR^{10}R^{18}$, NR^{10}, O and $S(O)_x$;

A_1 is selected from the group consisting of NR^{10}, O and S; and

D^2, G^2, L^2, M^2 and T^2 are independently selected from the group consisting of CR^{18} and N.

88. The compound of claim 87, wherein R^1 is selected from the group consisting of:

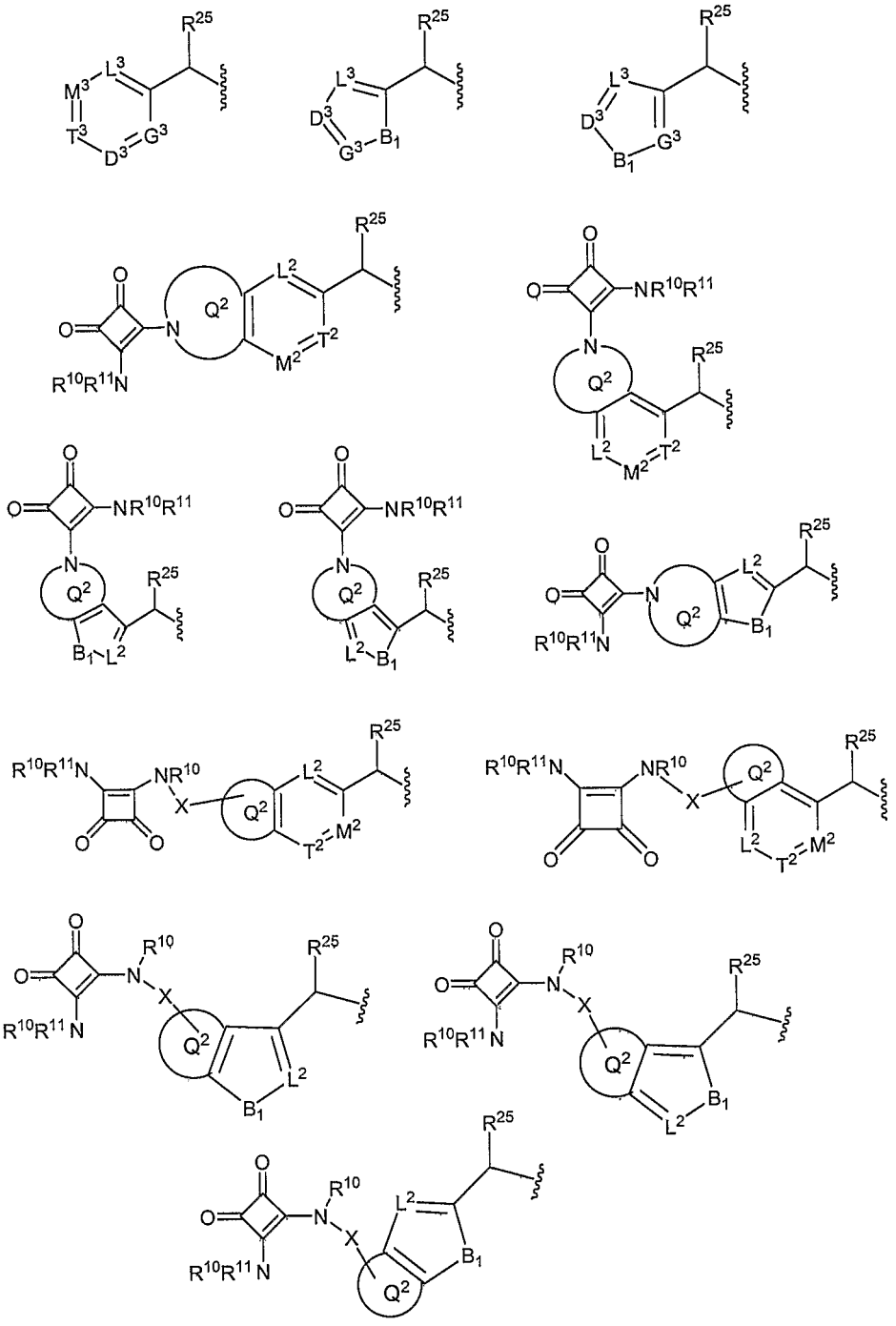




; and

.

89. The compound of claim 76, wherein R^1 is selected from the group consisting of:



wherein:

R^5 is independently selected from the group consisting of hydrogen, alkyl, $C(O)NR^{10}R^{11}$, aryl, arylalkyl, $SO_2NR^{10}R^{11}$ and $C(O)OR^{10}$ wherein alkyl, aryl and arylalkyl are optionally substituted one or more times;

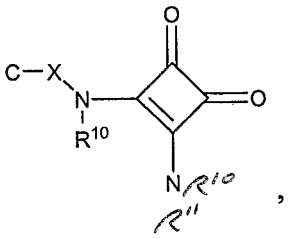
R^{18} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{19} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two R^{19} groups together at one carbon atom form =O, =S or $=NR^{10}$;

R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $CONR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl and haloalkyl are optionally substituted one or more times;

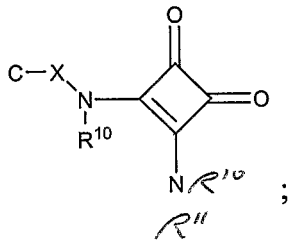
L^2, M^2, and T^2 are independently selected from the group consisting of CR^{18} and N;

L^3, M^3, T^3, D^3, and G^3 are independently selected from N, CR^{18}, and



,

with the provision that one of L^3, M^3, T^3, D^3, and G^3 is

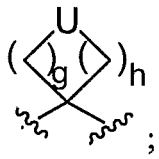


;

B_1 is selected from the group consisting of NR^{10}, O and S;

X is selected from the group consisting of a bond and $(CR^{10}R^{11})_wE(CR^{10}R^{11})_w$

E is selected from the group consisting of a bond, $CR^{10}R^{11}$, O, NR^5, S, S=O, $S(=O)_2$, C(=O), $N(R^{10})(C=O)$, $(C=O)N(R^{10})$, $N(R^{10})S(=O)_2$, $S(=O)_2N(R^{10})$, C=N-OR^{11}, $-C(R^{10}R^{11})C(R^{10}R^{11})-$, $-CH_2-W^1-$ and



;

W^1 is selected from the group consisting of O, NR^5, S, S=O, $S(=O)_2$, $N(R^{10})(C=O)$, $N(R^{10})S(=O)_2$ and $S(=O)_2N(R^{10})$;

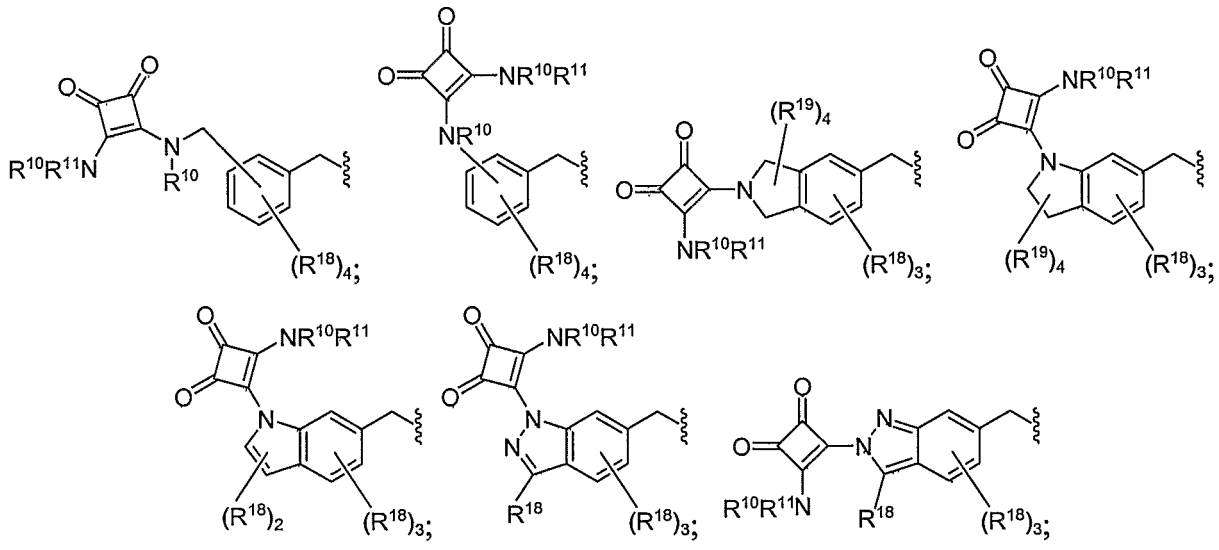
U is selected from $C(R^5R^{10})$, NR^5, O, S, S=O, $S(=O)_2$;

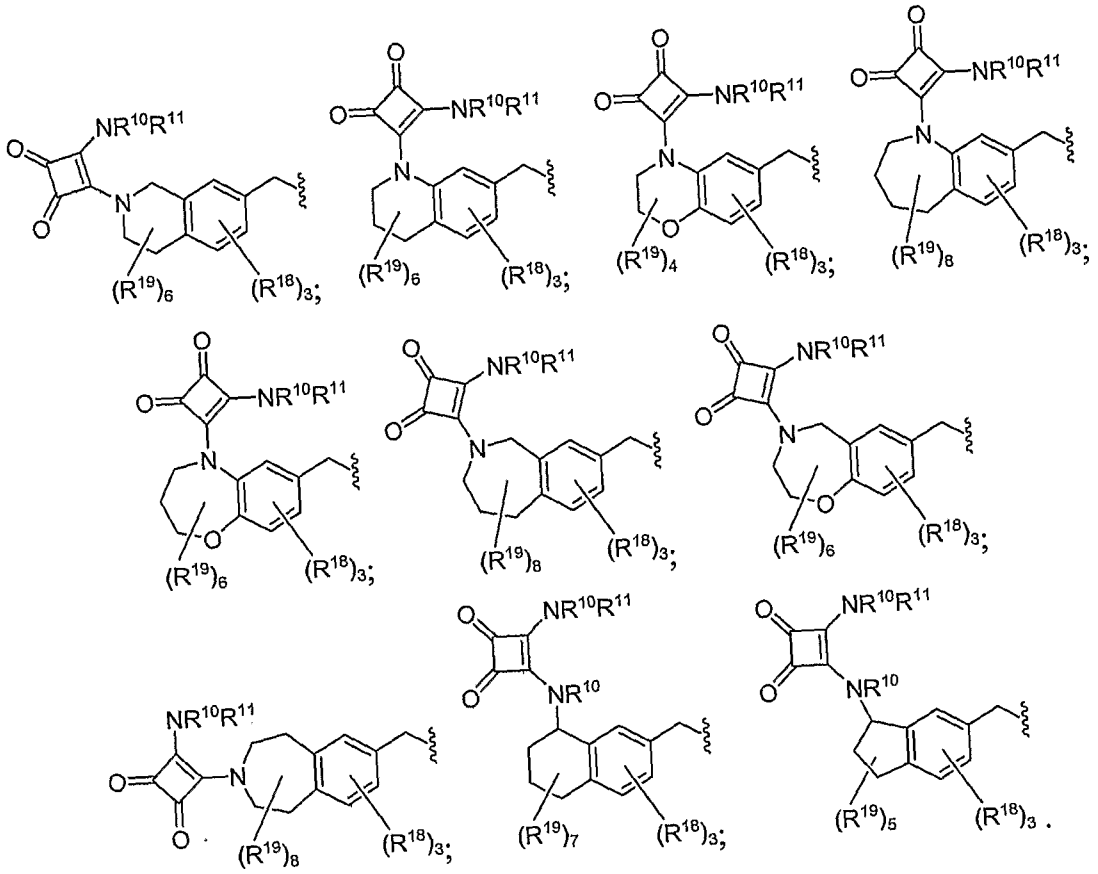
g and h are independently selected from 0-2;

w is selected from 0-4; and

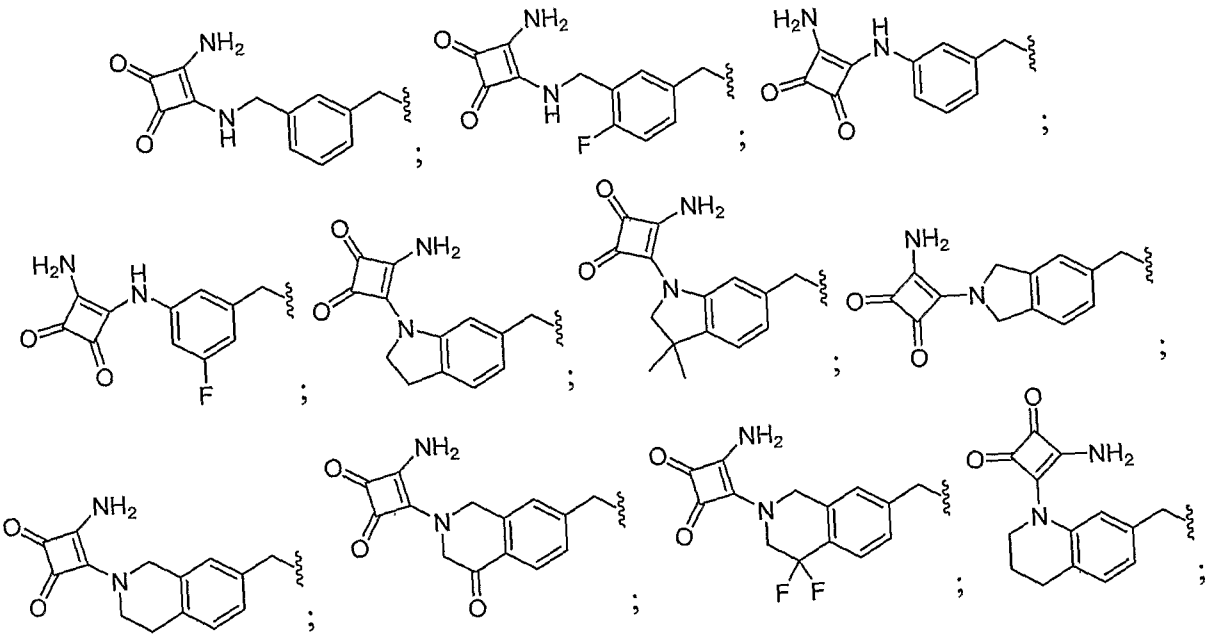
Q^2 is a 5- to 8-membered ring consisting of cycloalkyl, heterocycloalkyl, aryl, heteroaryl, which is optionally substituted one or more times with R^{19}.

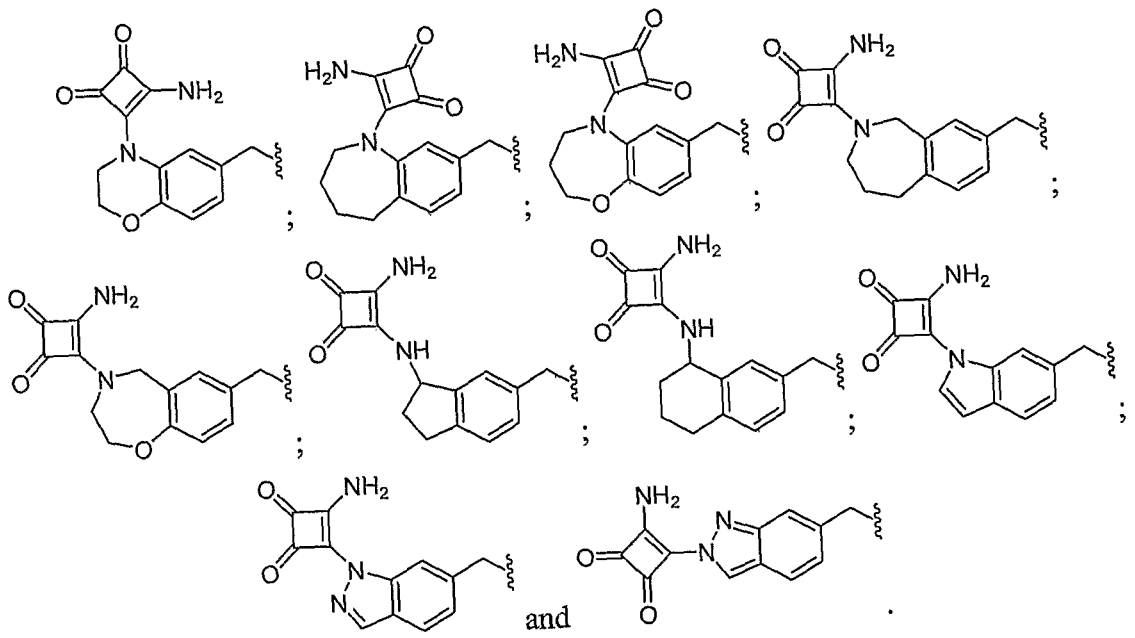
90. The compound of claim 89, wherein R^1 is selected from the group consisting of:



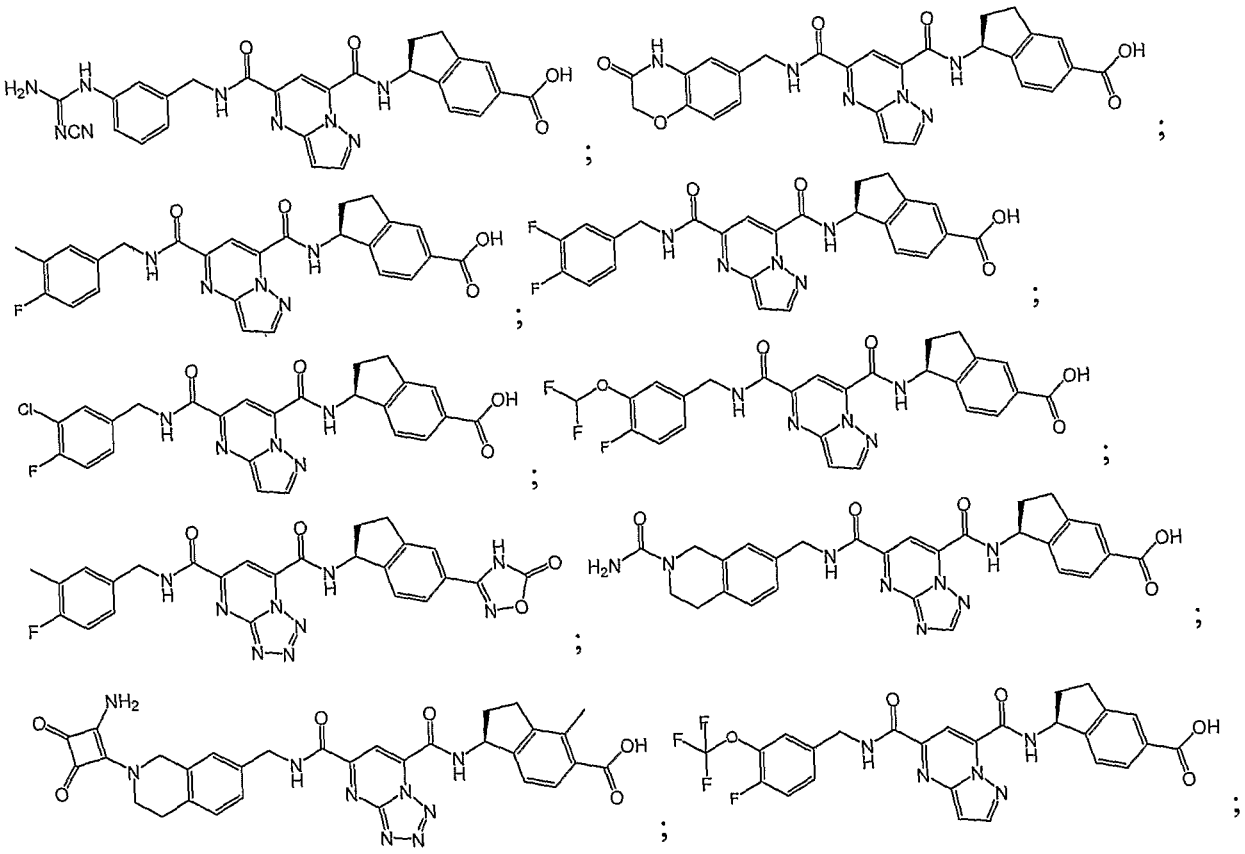


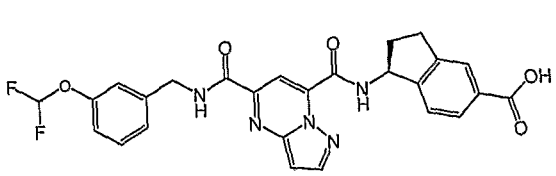
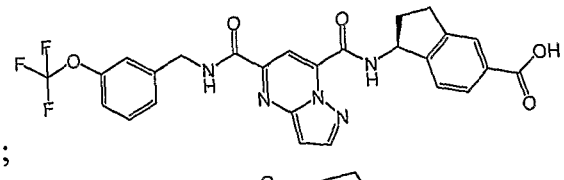
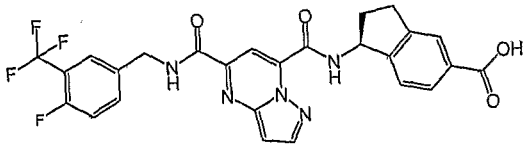
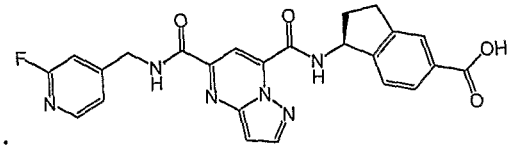
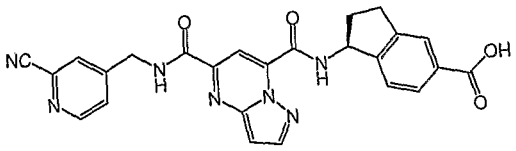
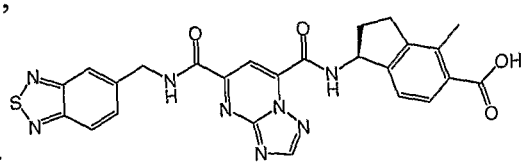
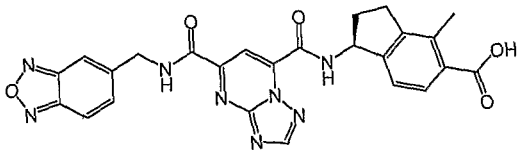
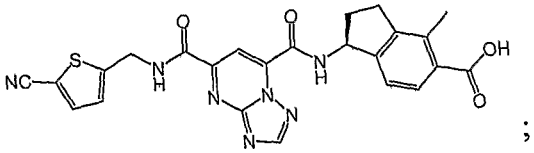
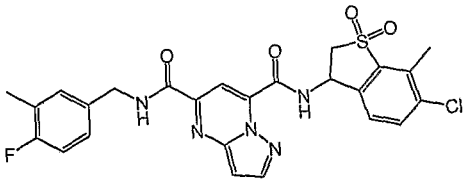
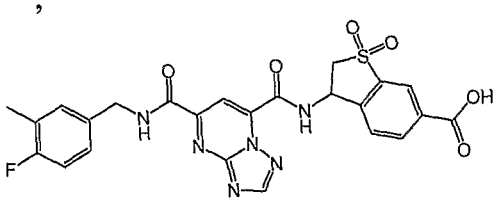
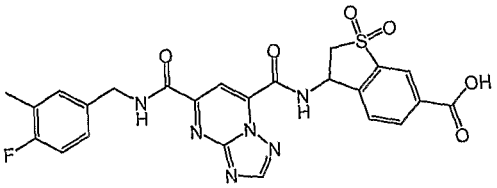
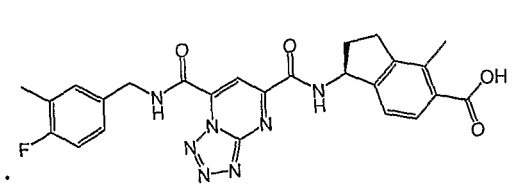
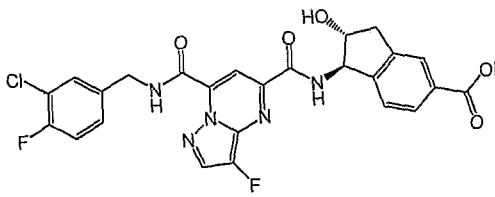
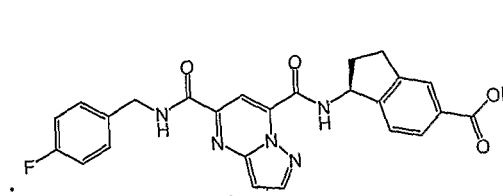
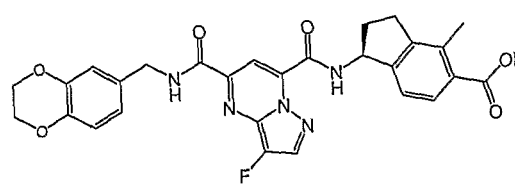
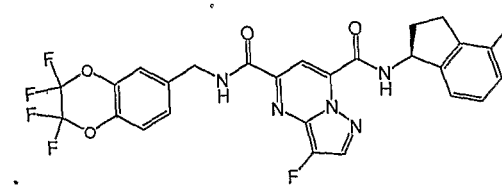
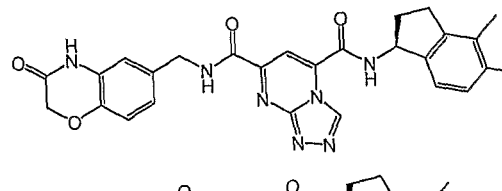
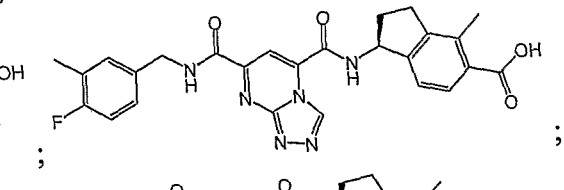
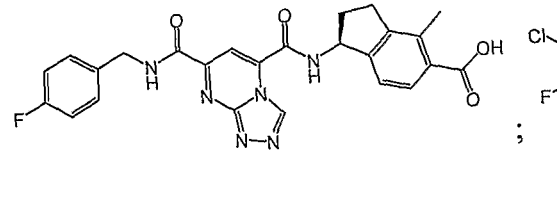
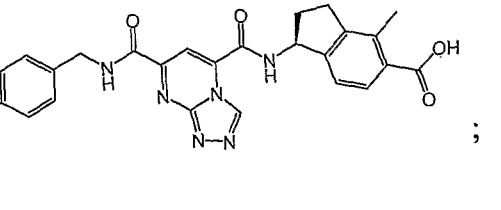
91. The compound of claim 89, wherein R^1 is selected from the group consisting of:





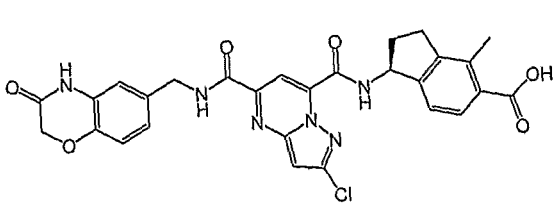
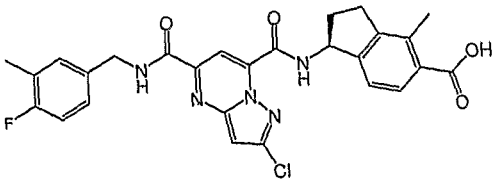
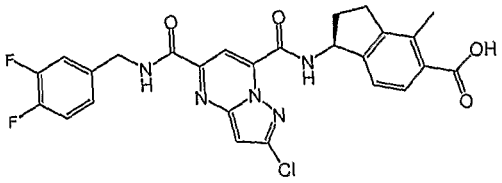
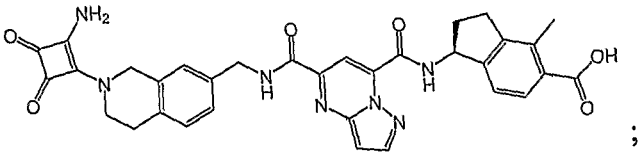
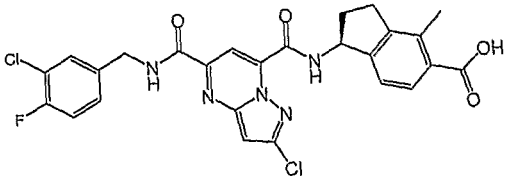
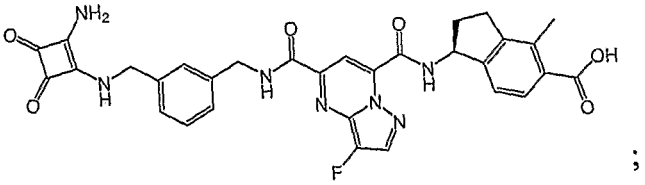
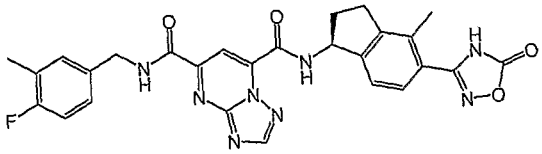
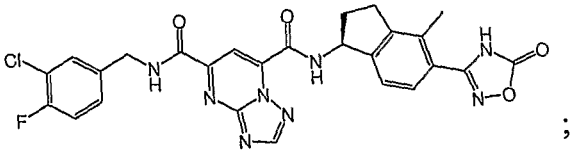
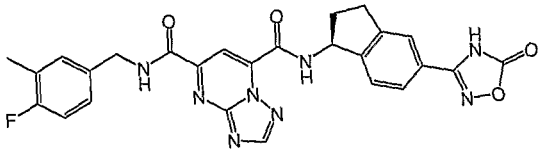
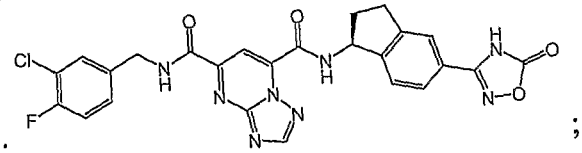
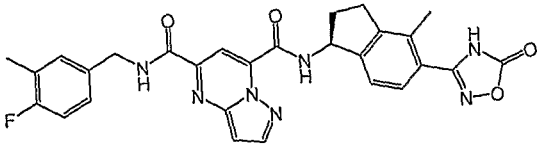
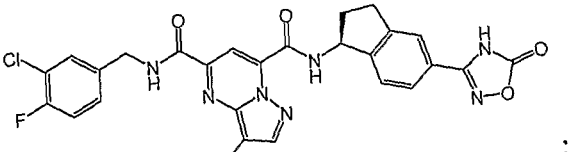
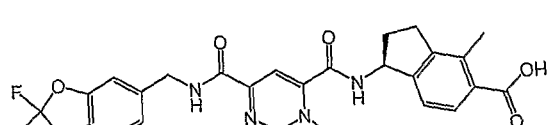
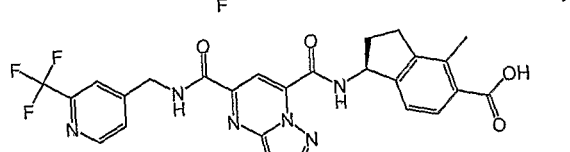
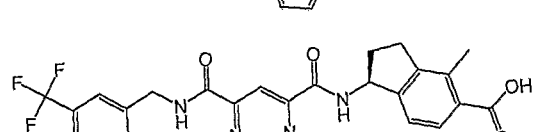
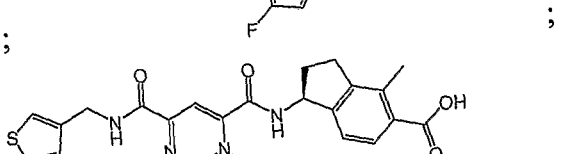
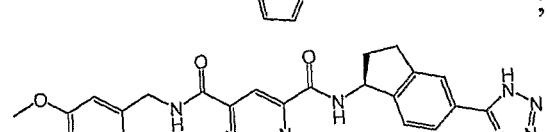
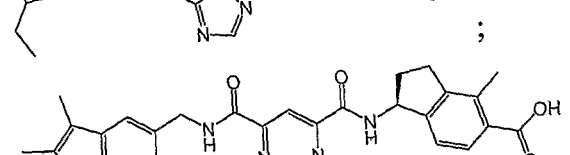
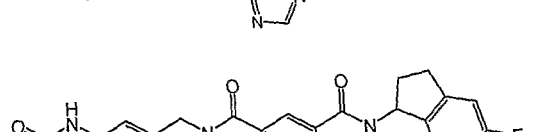
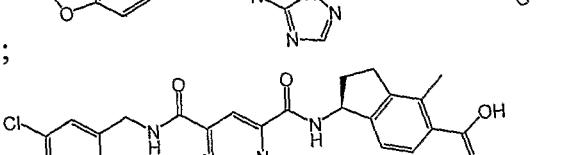
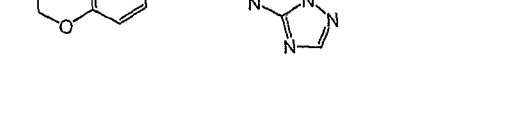
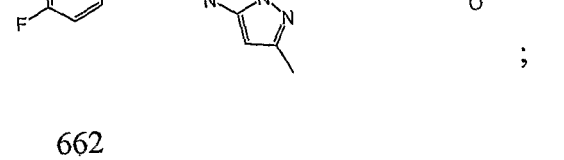
92. A compound selected from the group consisting of:

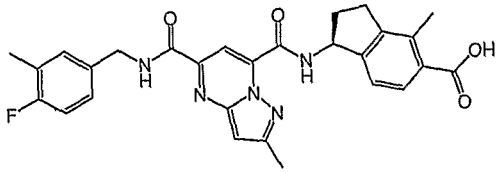
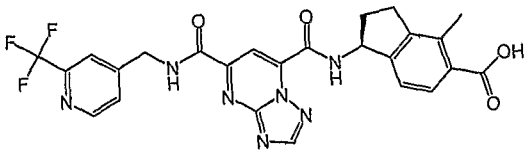
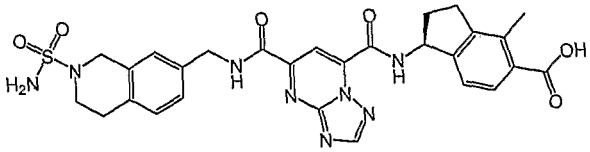
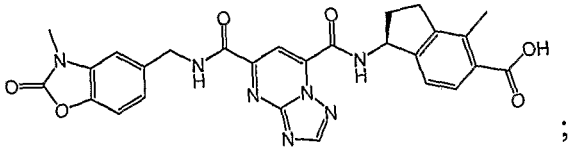
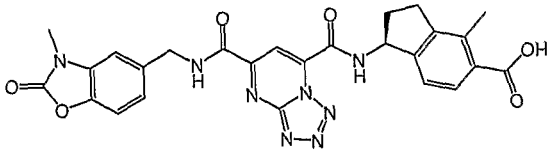
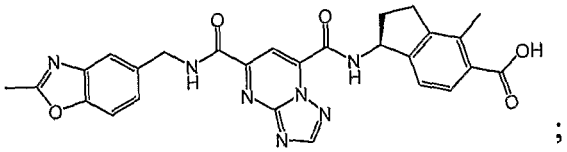
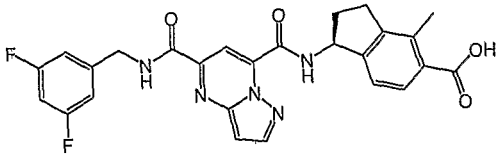
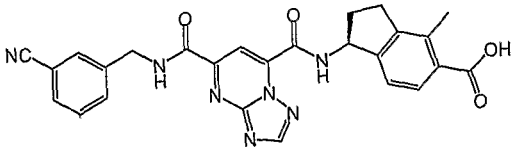
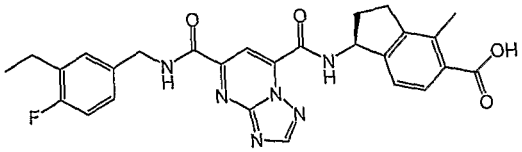
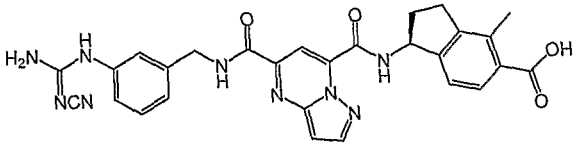
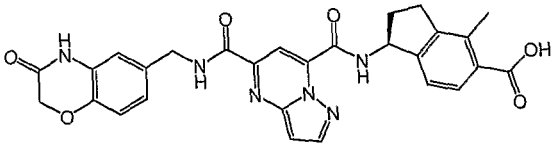
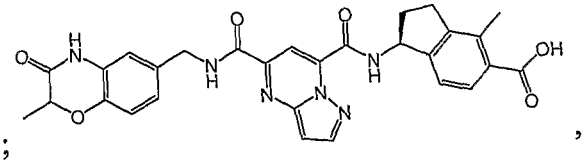
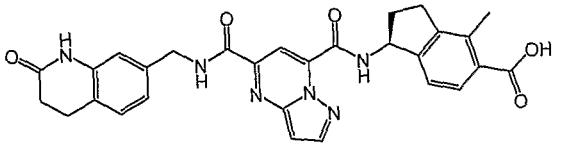
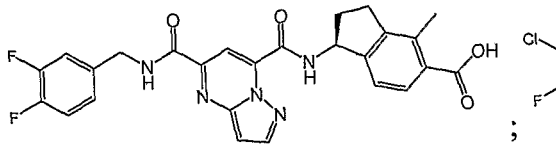
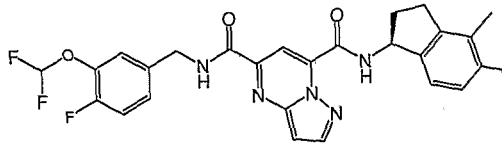
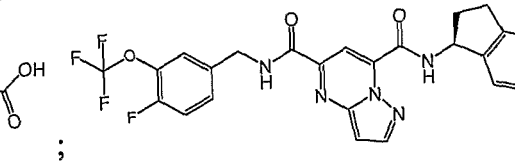
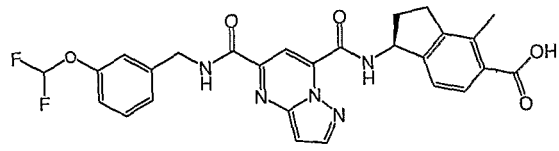
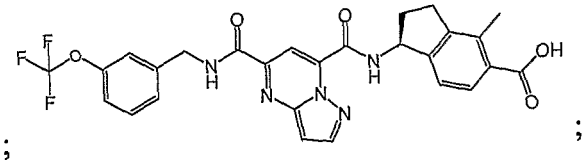
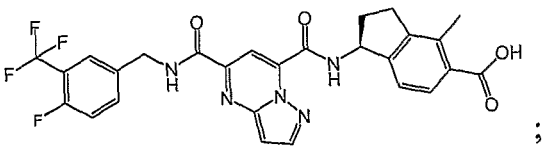
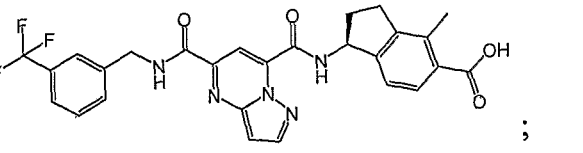



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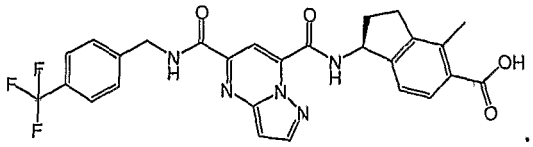
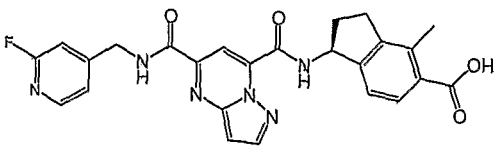
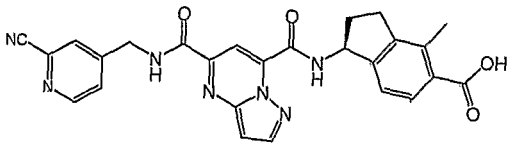
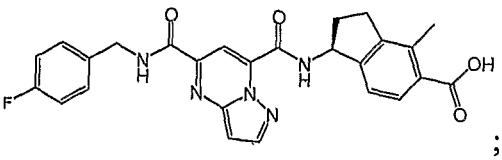
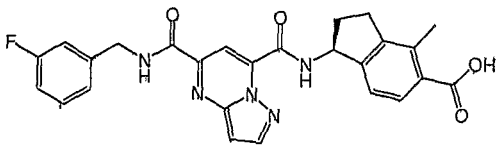
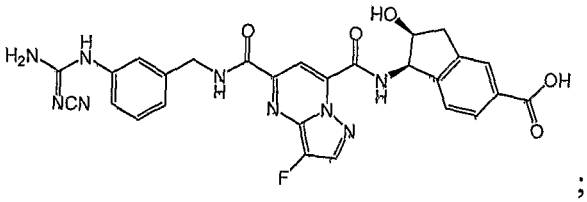
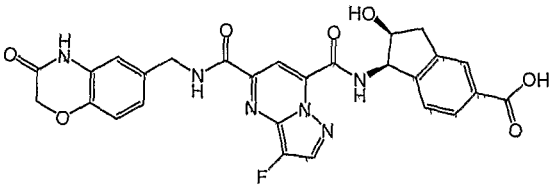
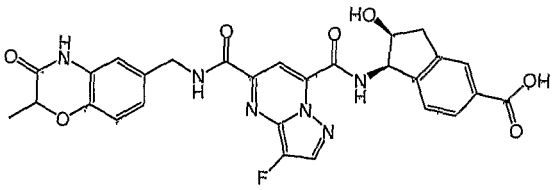
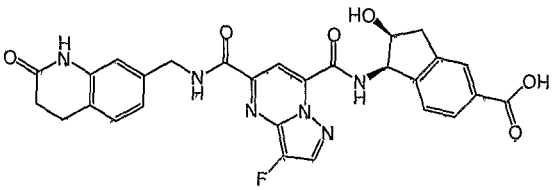
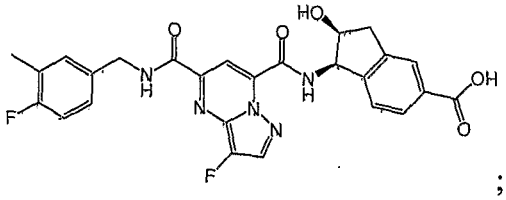
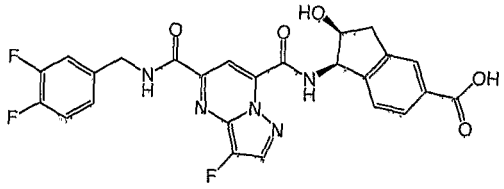
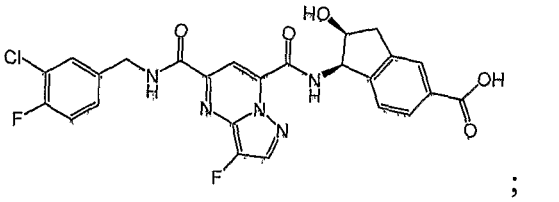
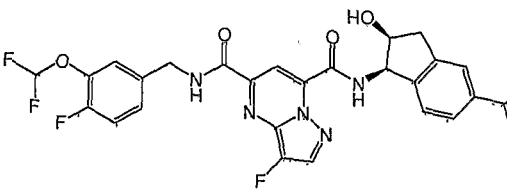
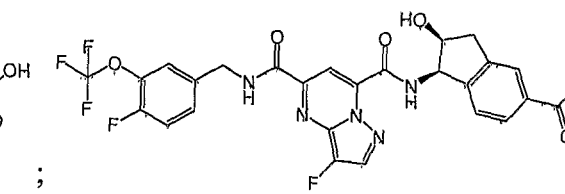
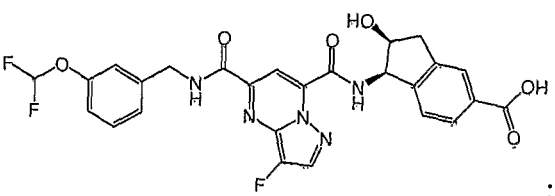
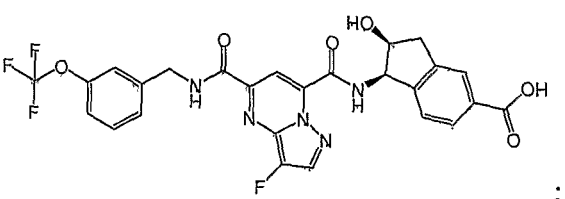
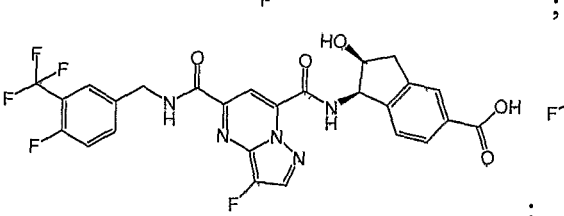
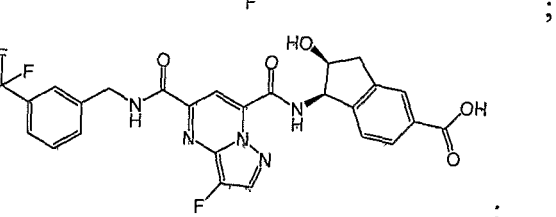
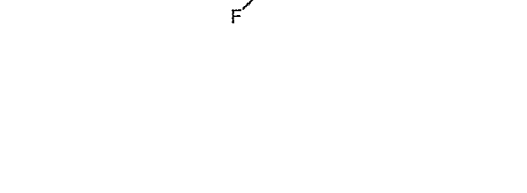
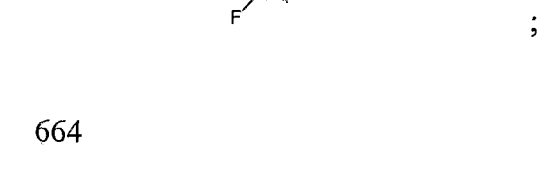
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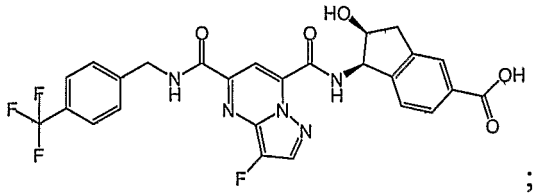
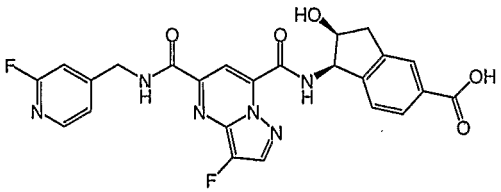
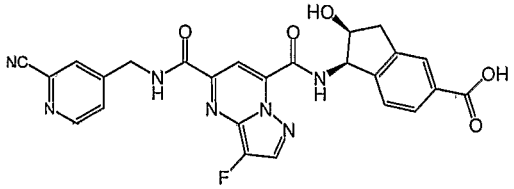
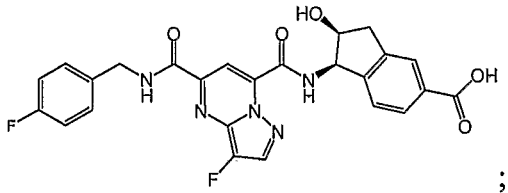
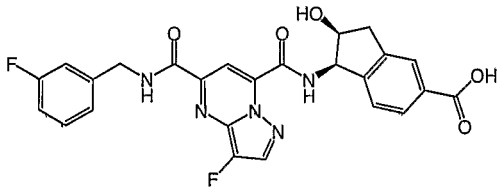
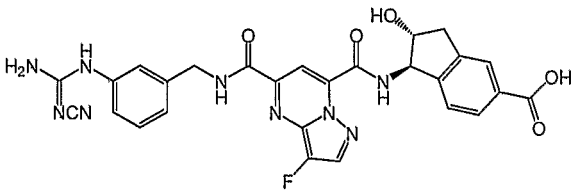
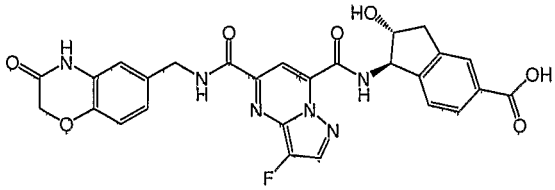
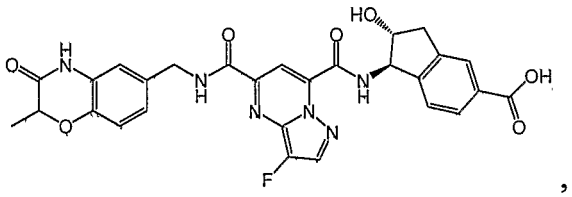
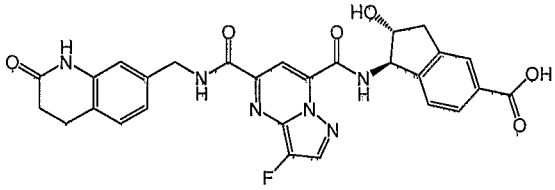
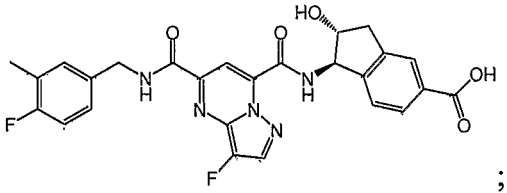
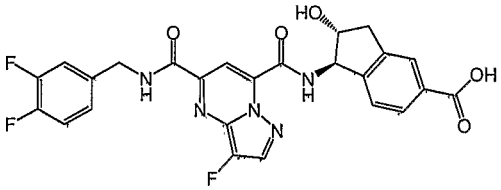
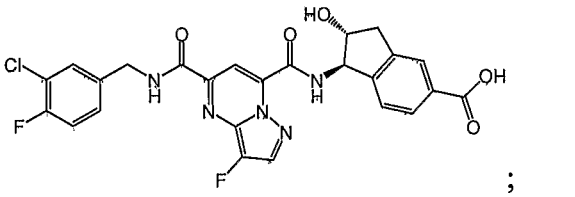
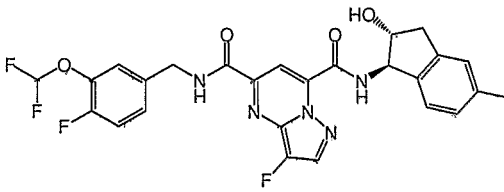
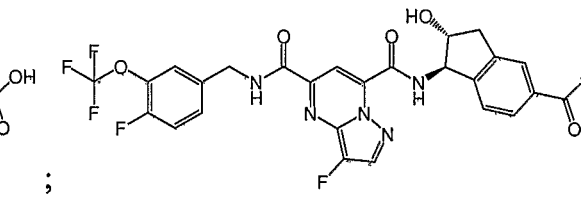
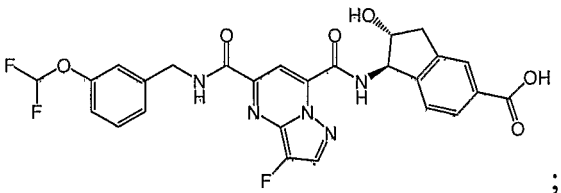
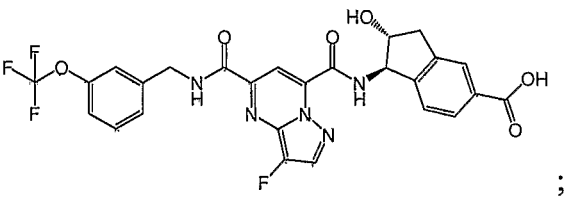

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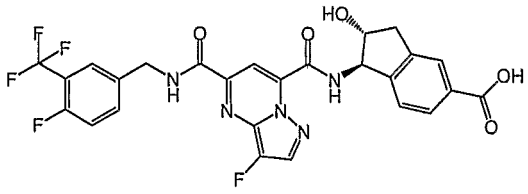
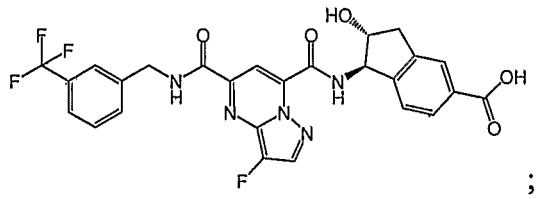
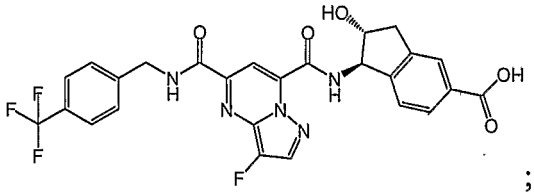
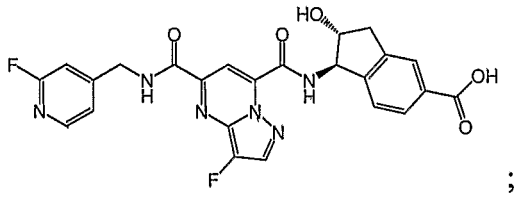
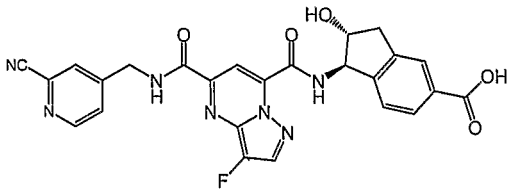
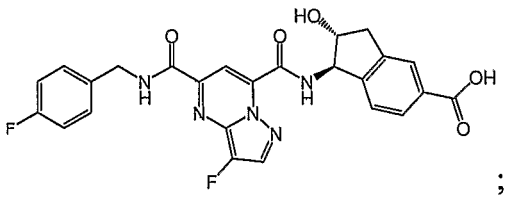
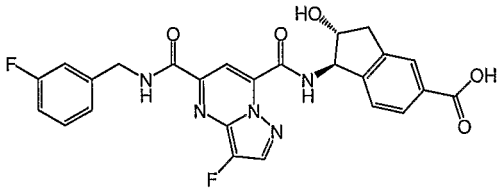
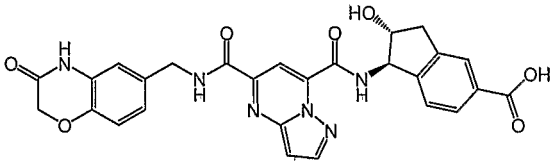
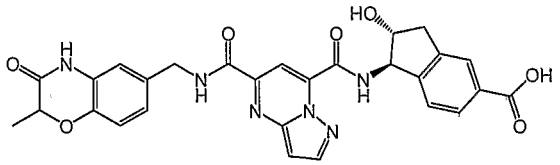
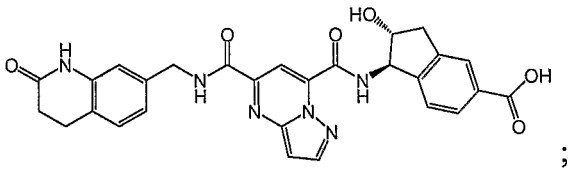
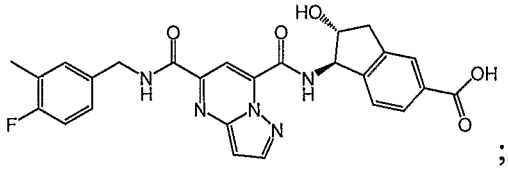
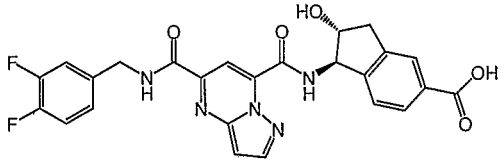
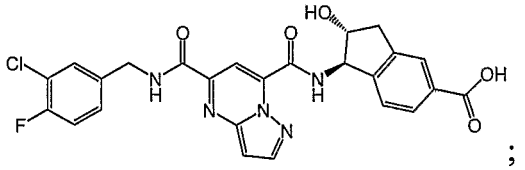
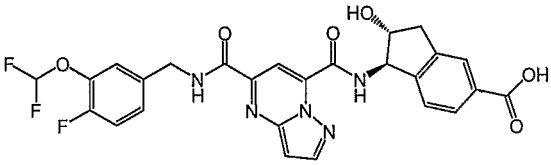
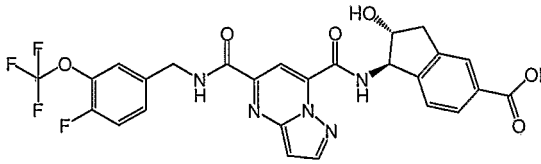
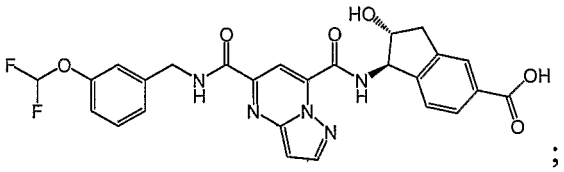
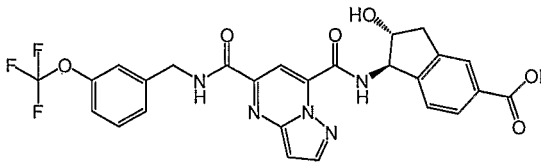
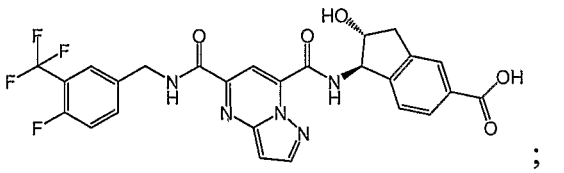
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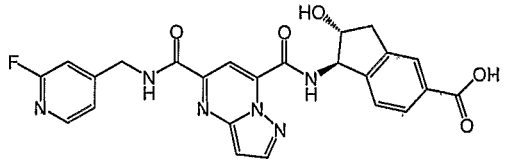
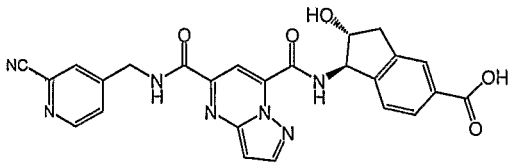
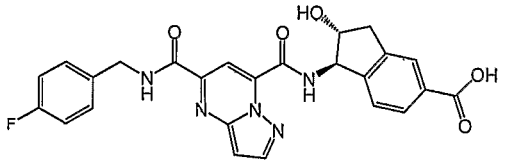
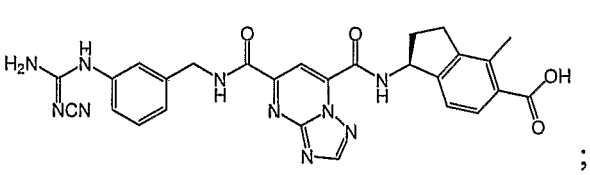
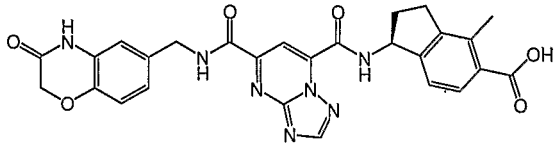
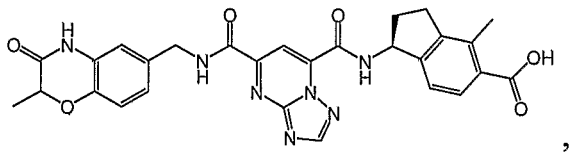
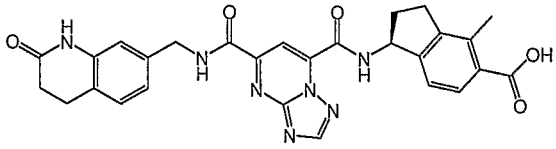
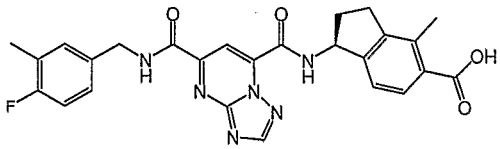
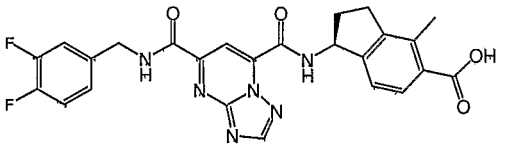
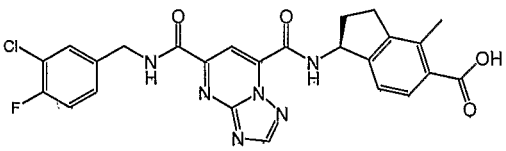
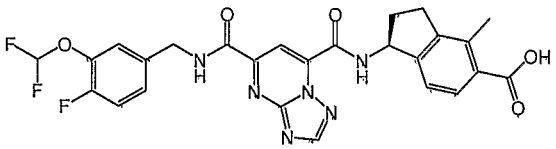
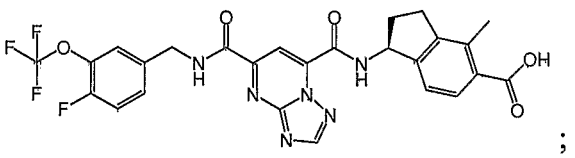
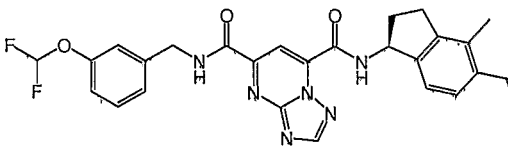
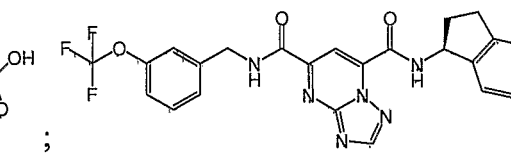
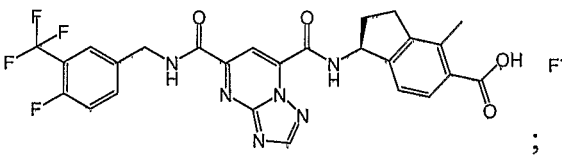
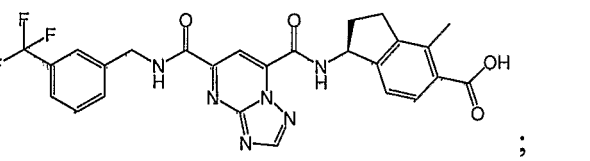
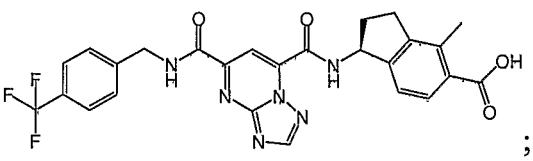
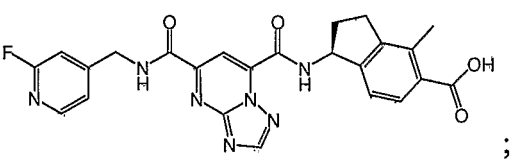
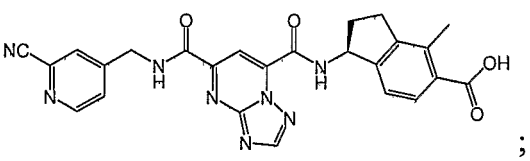
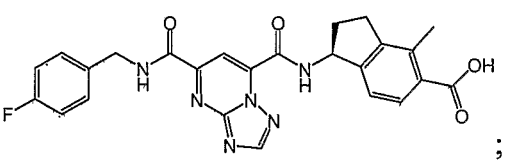

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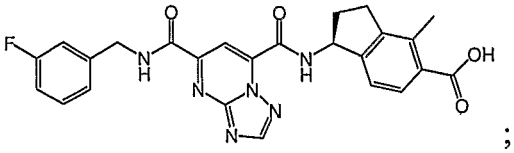
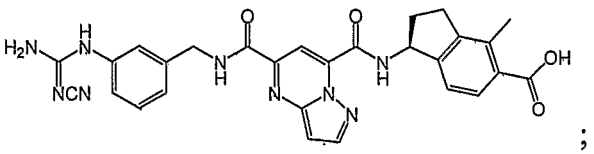
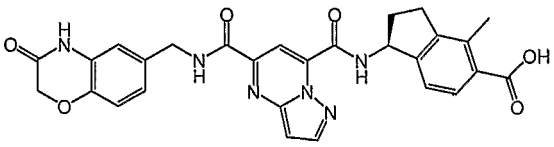
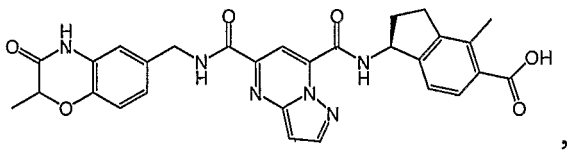
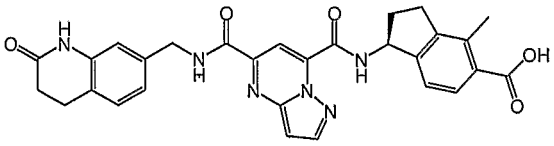
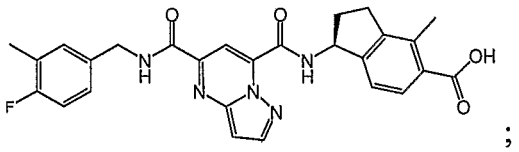
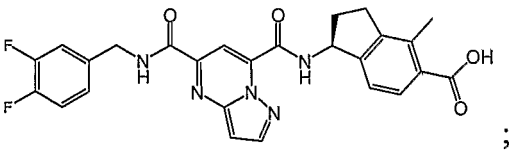
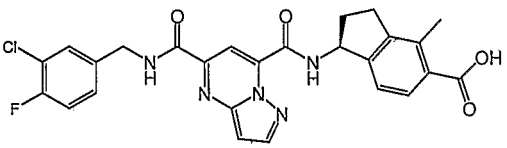
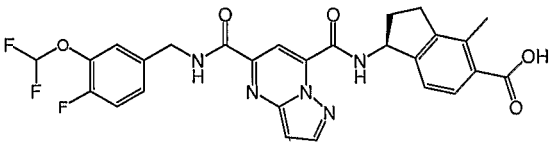
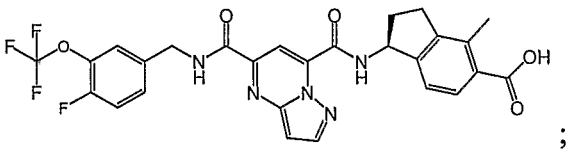
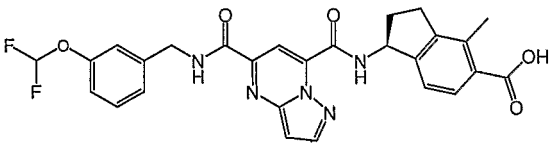
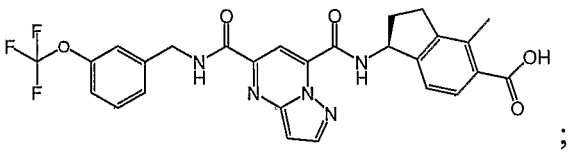
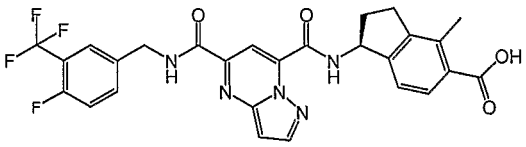
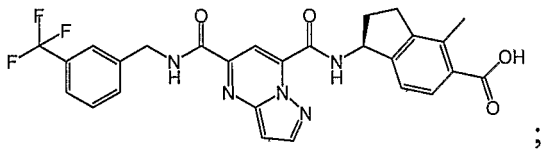
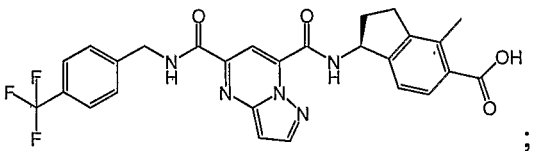
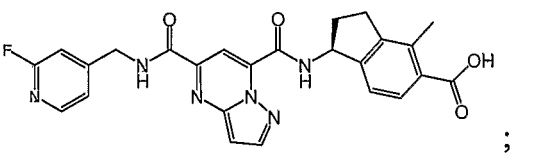
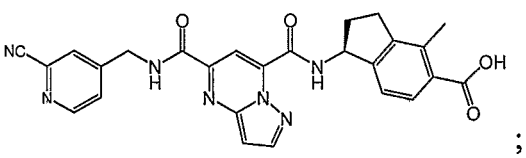
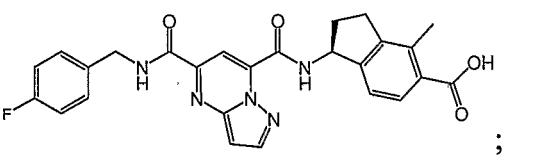
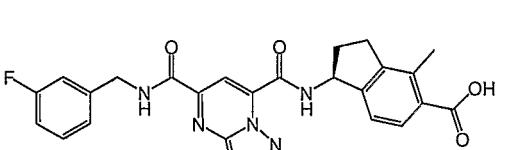
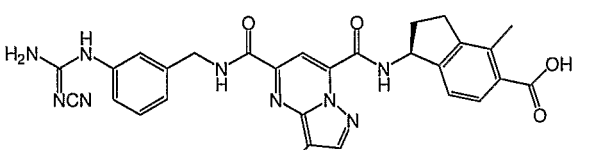
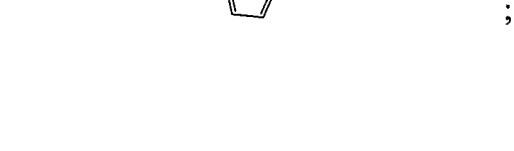
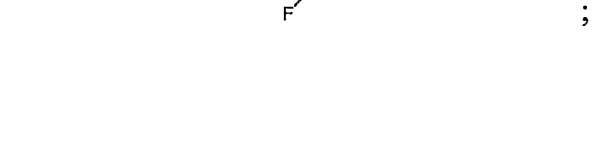
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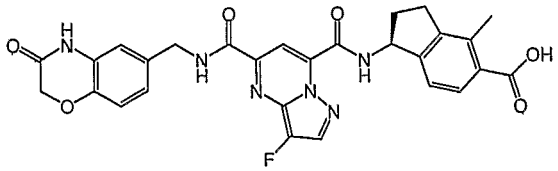
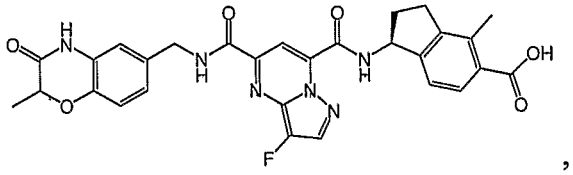
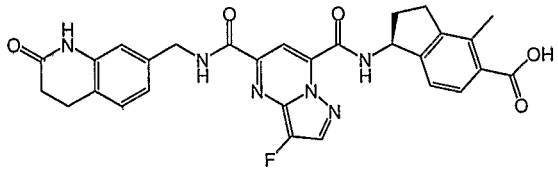
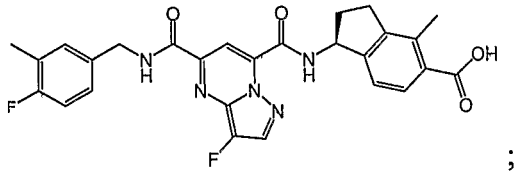
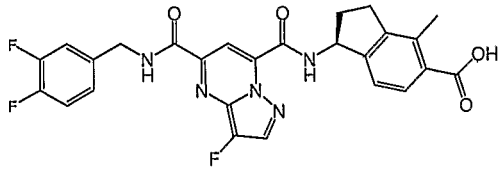
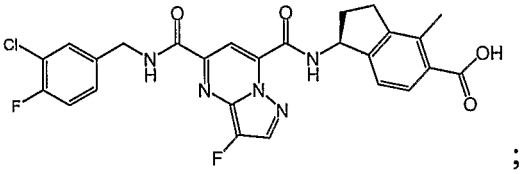
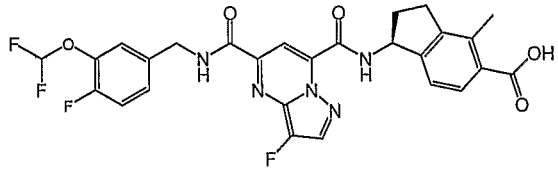
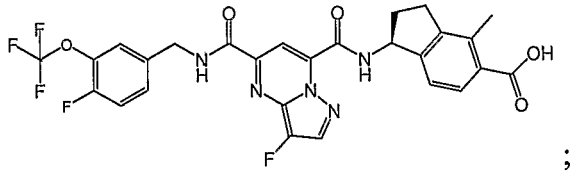
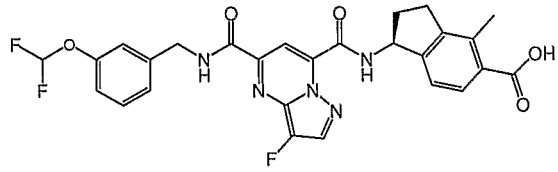
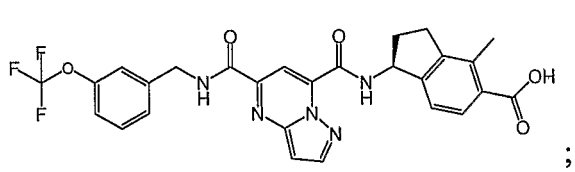
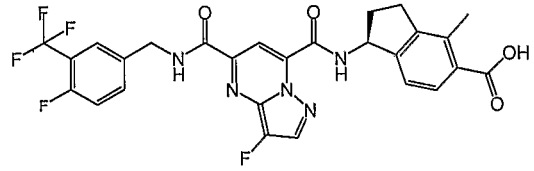
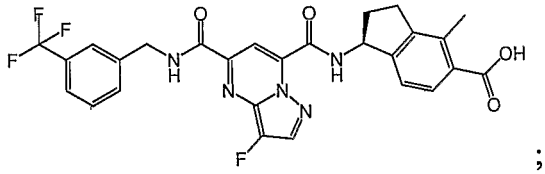
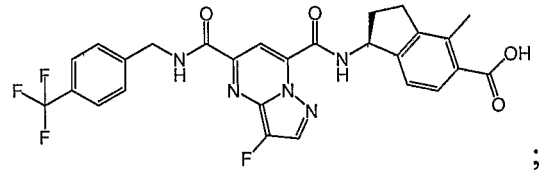
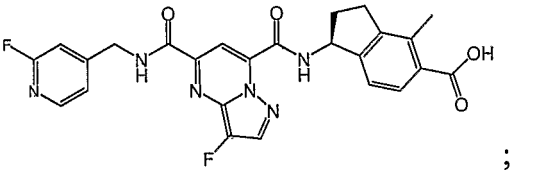
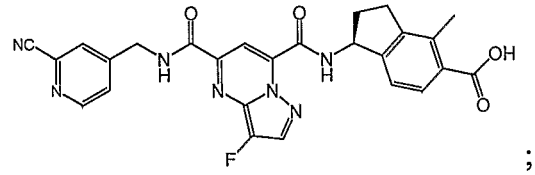
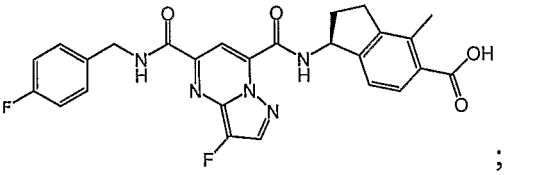
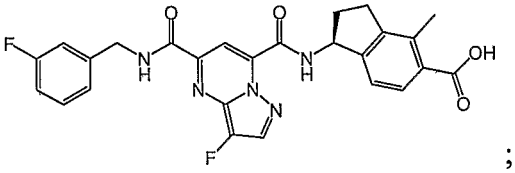

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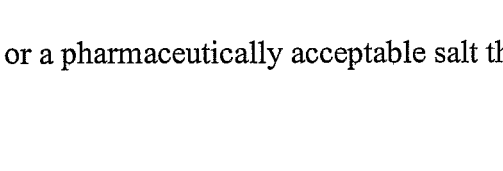

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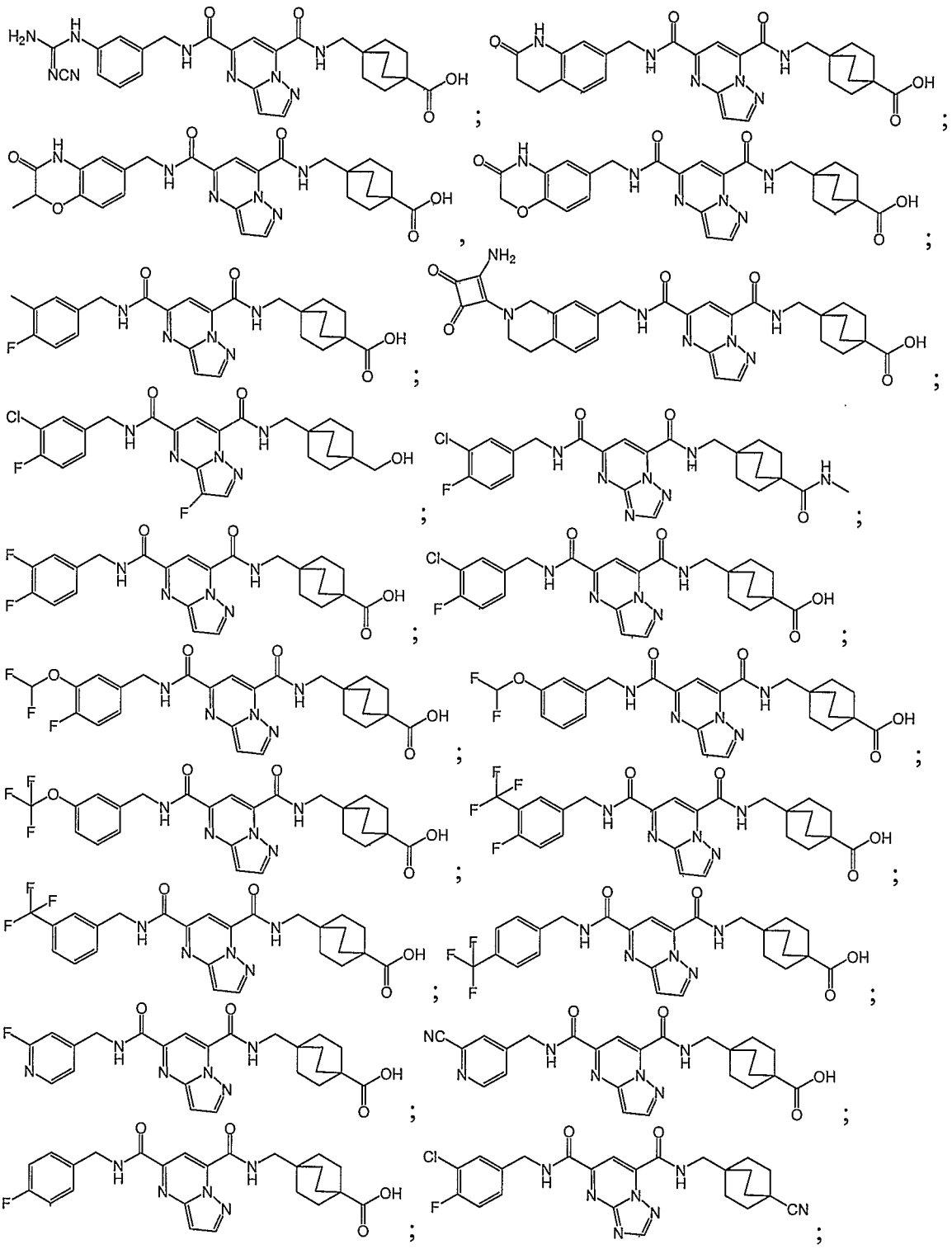

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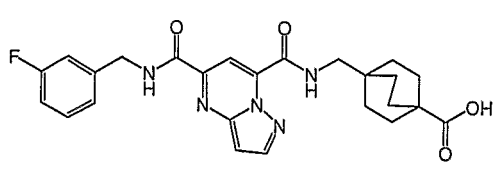
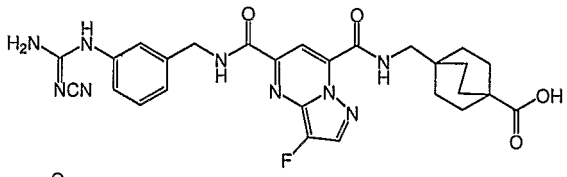
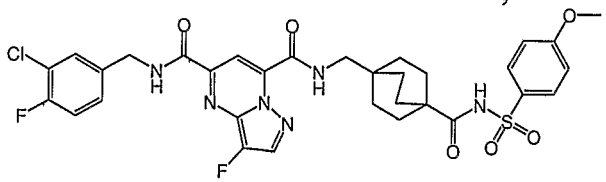
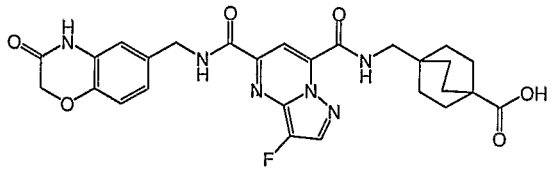
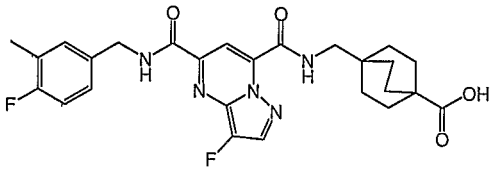
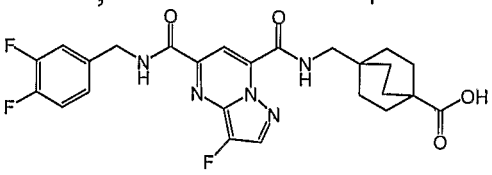
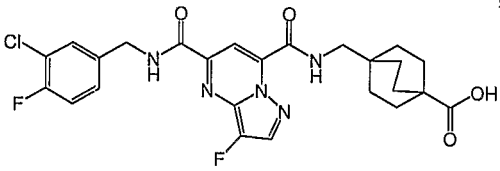
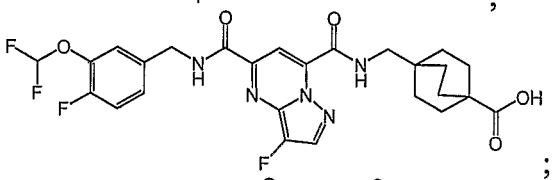
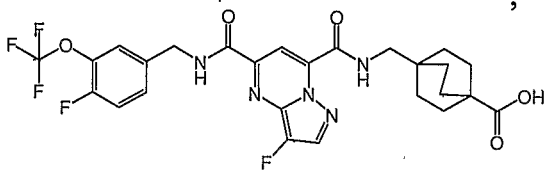
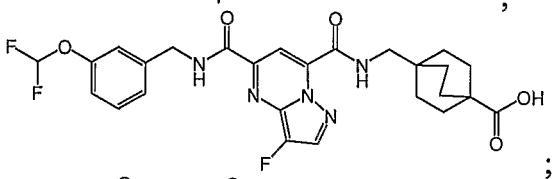
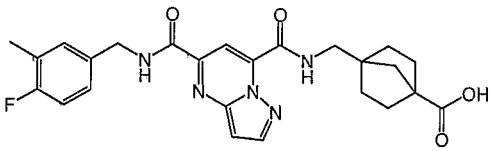
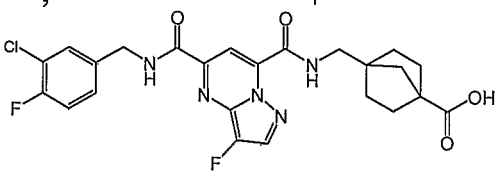
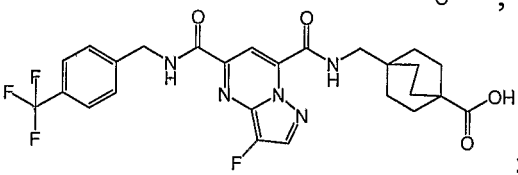
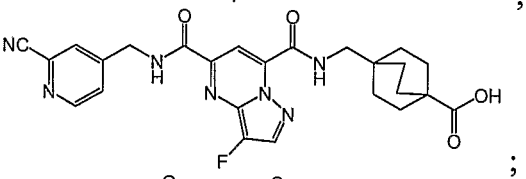
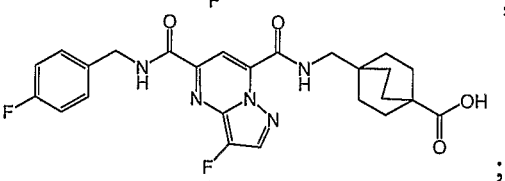
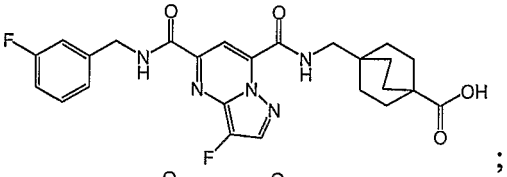
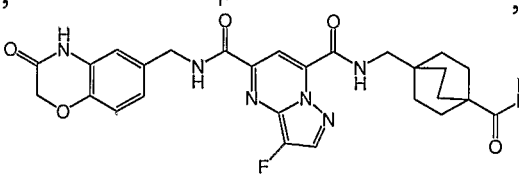
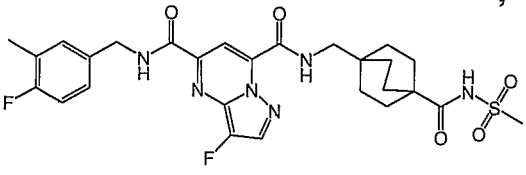
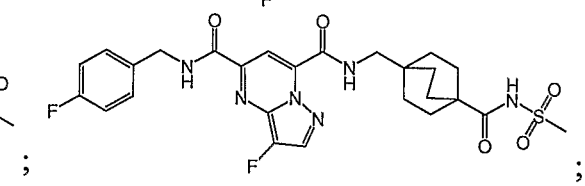

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or a pharmaceutically acceptable salt thereof.

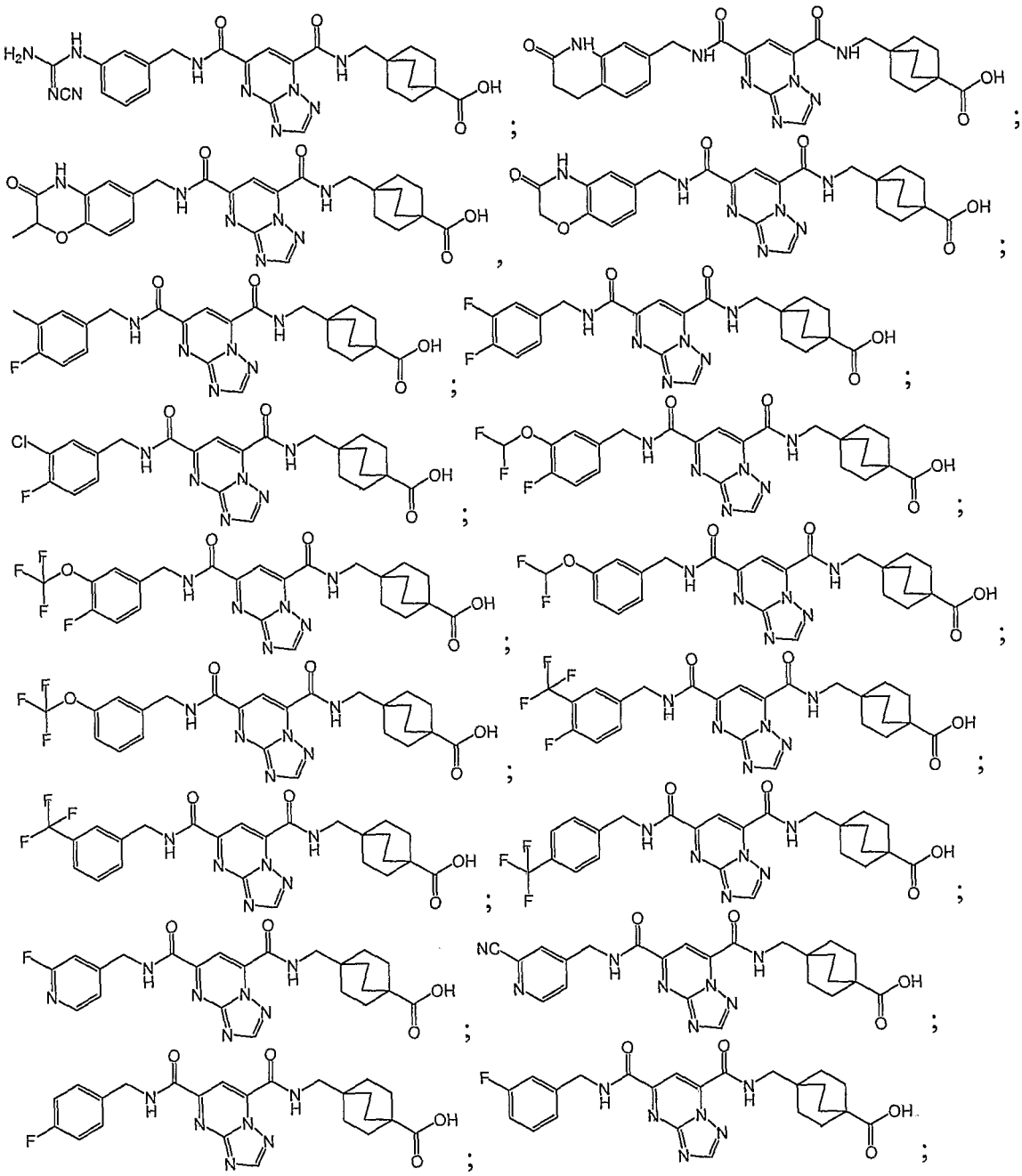
93. A compound selected from the group consisting of:




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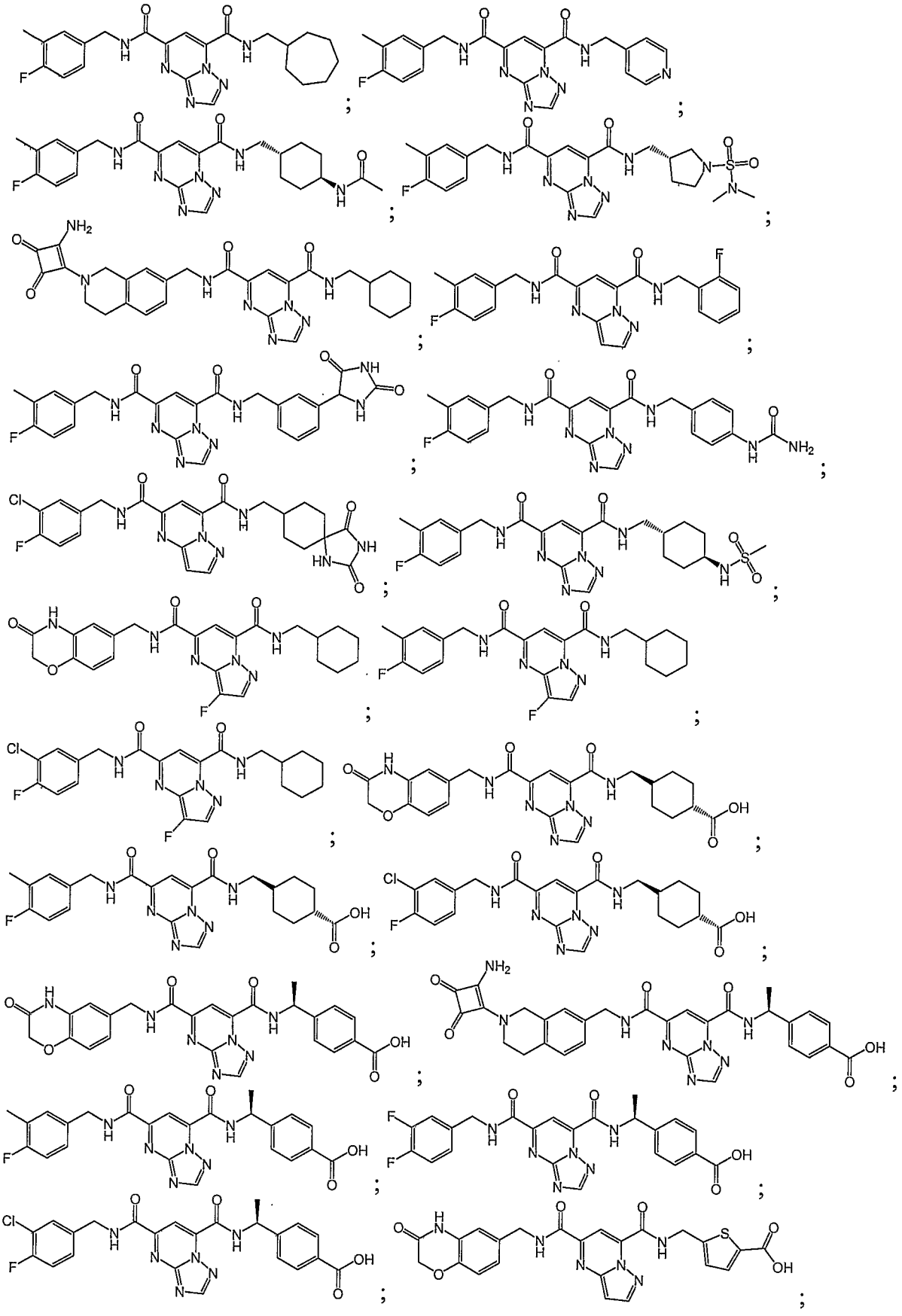
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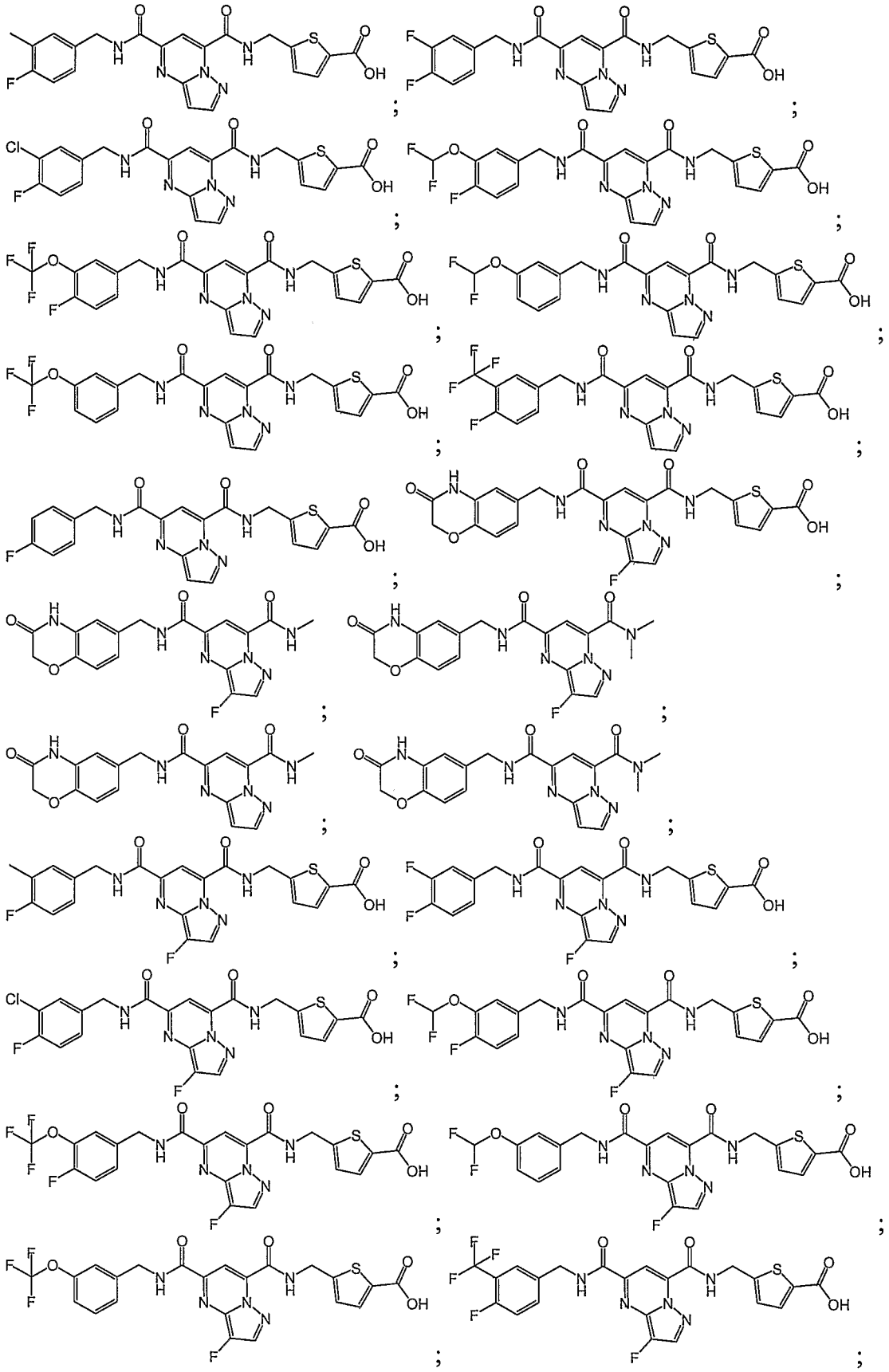
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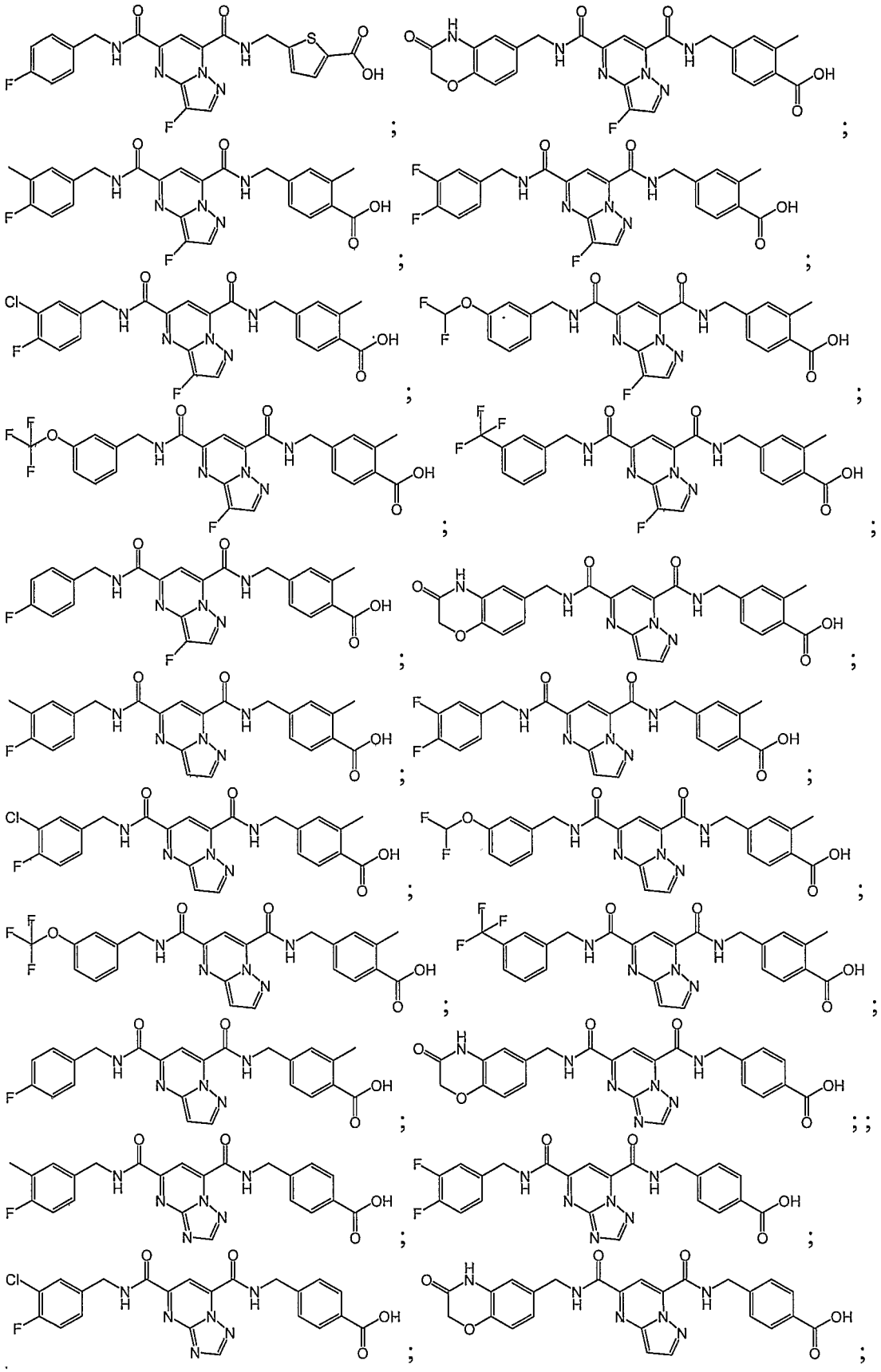


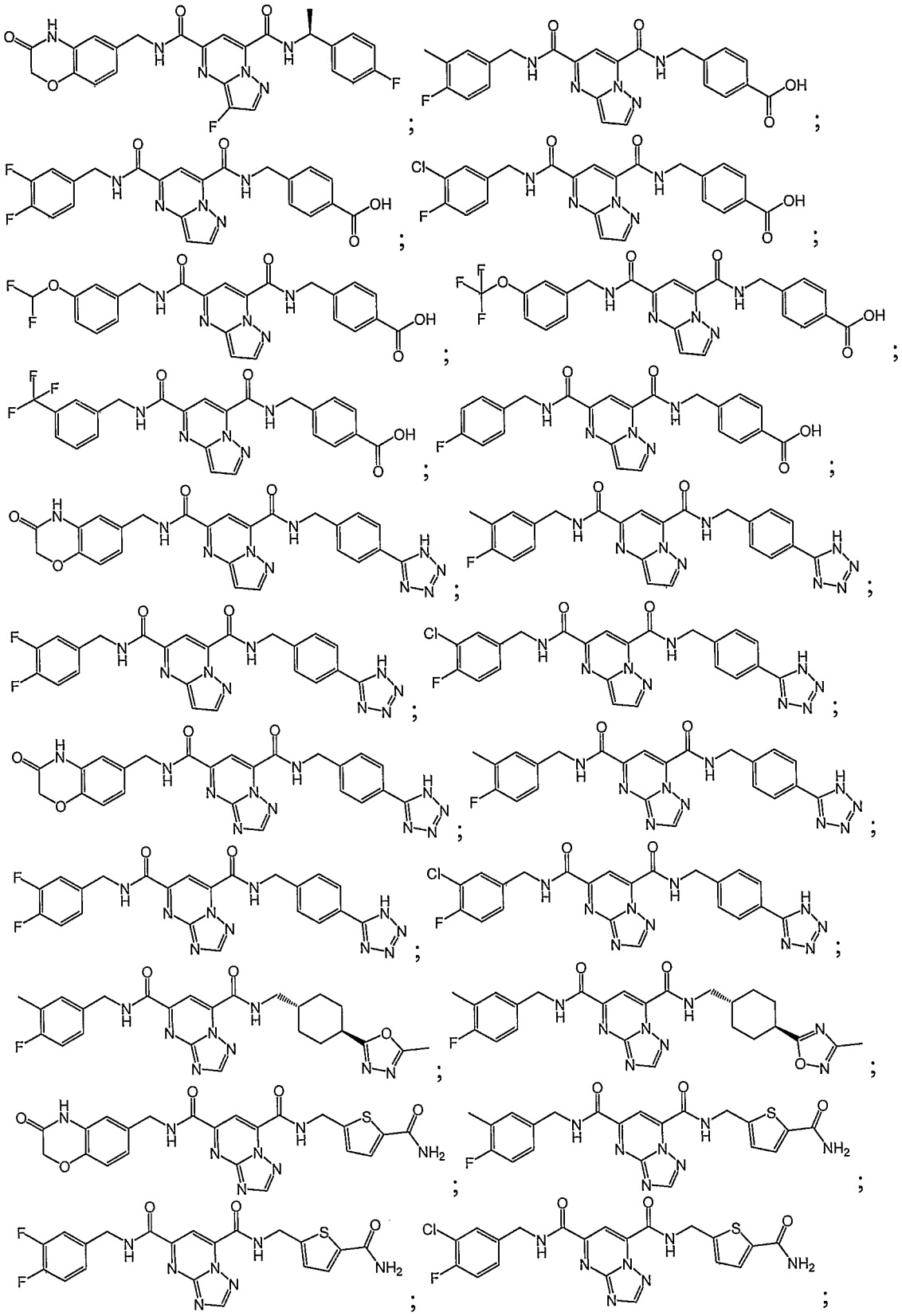
or a pharmaceutically acceptable salt thereof.

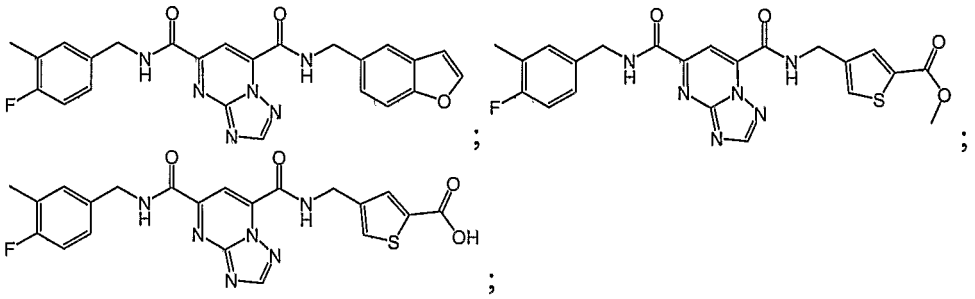
94. A compound selected from the group consisting of:





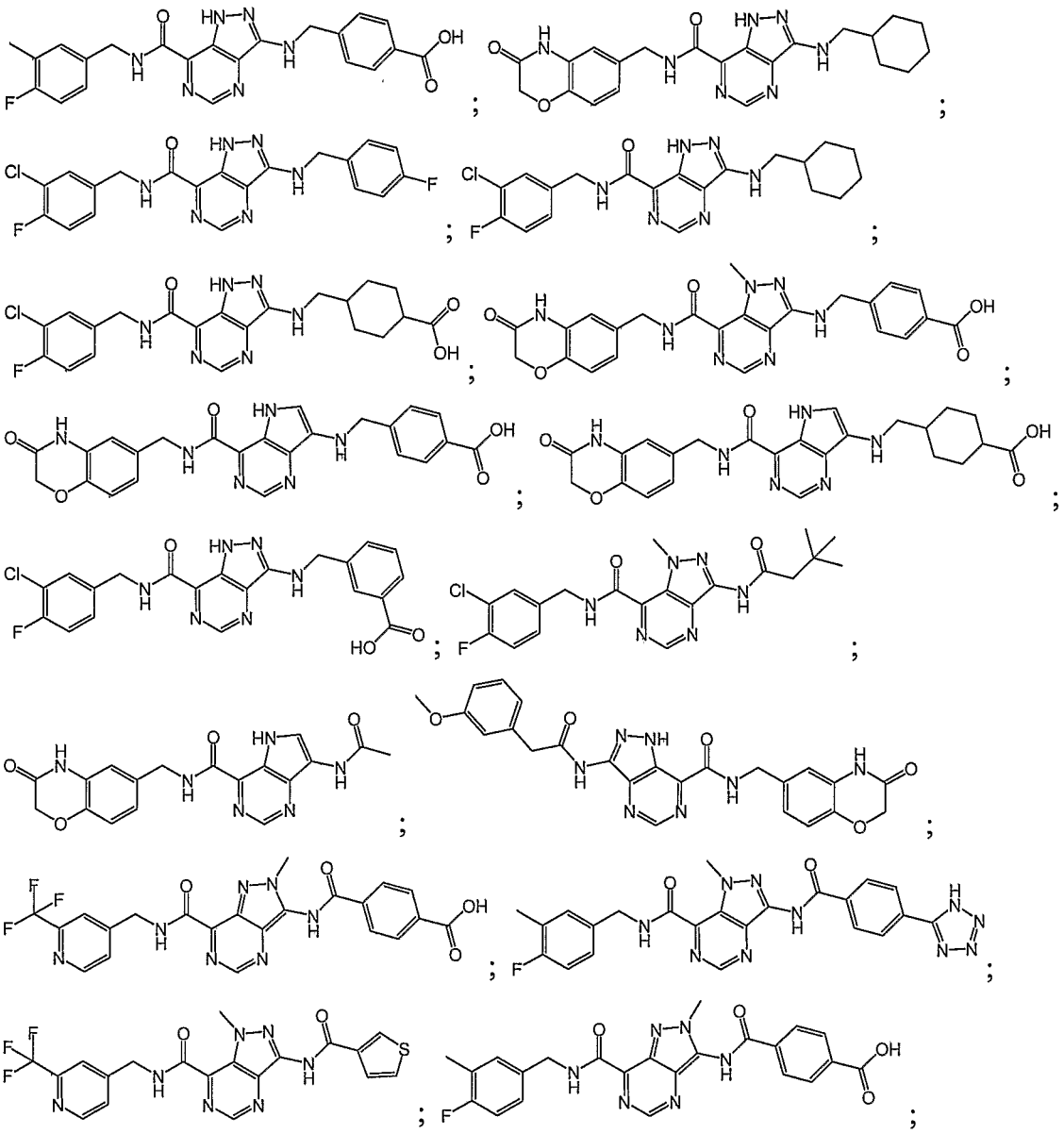


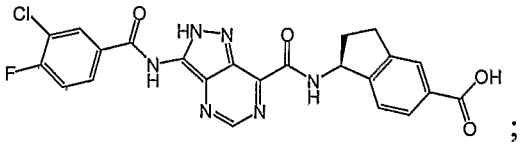
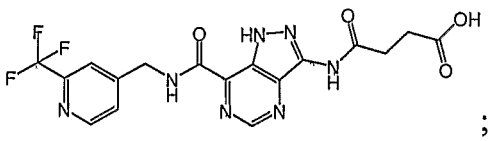
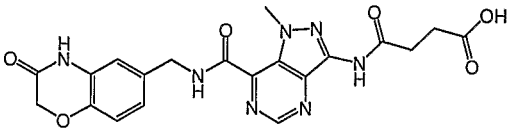
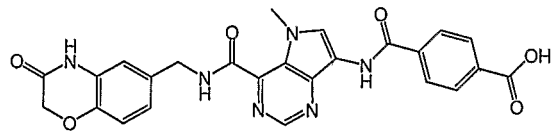
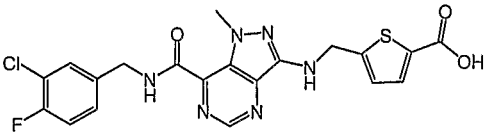
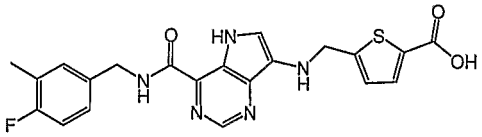
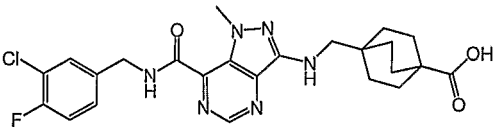
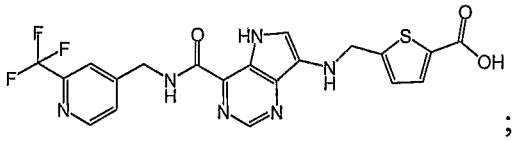
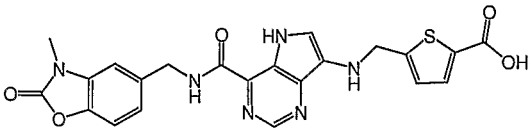
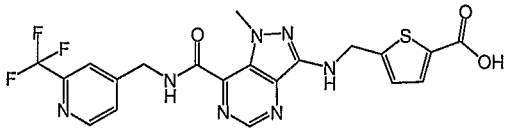
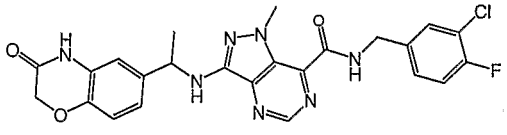
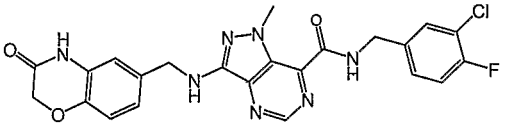
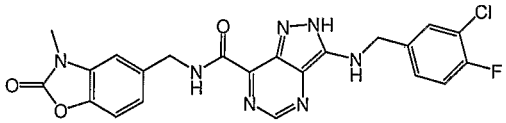
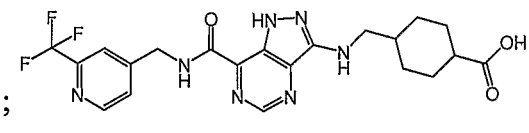
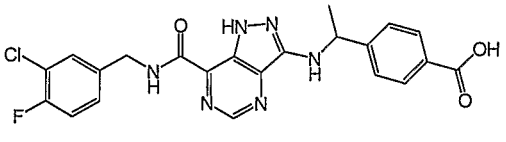
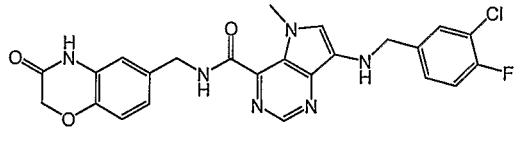
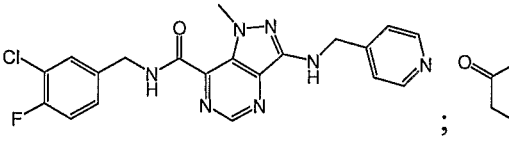
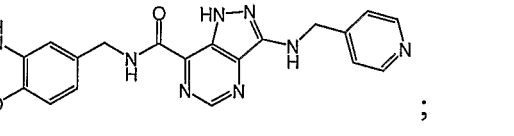
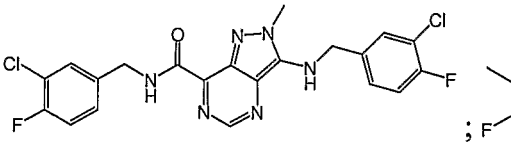
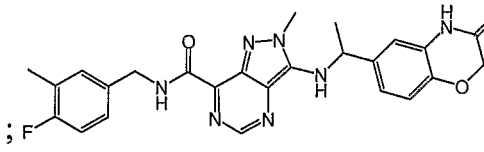
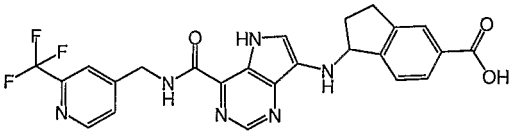
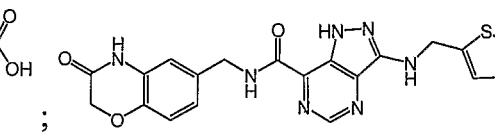




or a pharmaceutically acceptable salt thereof.

95. A compound selected from the group consisting of



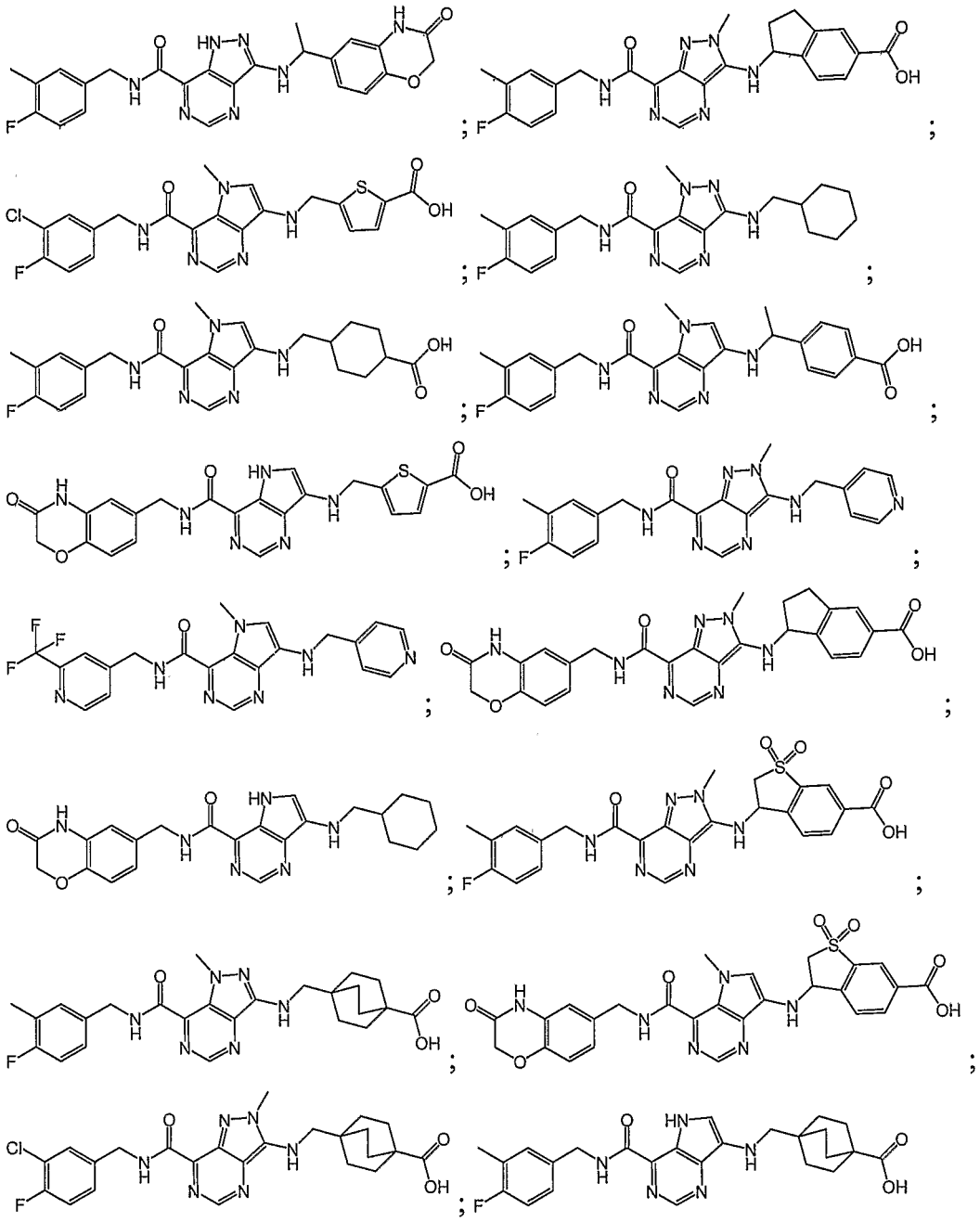

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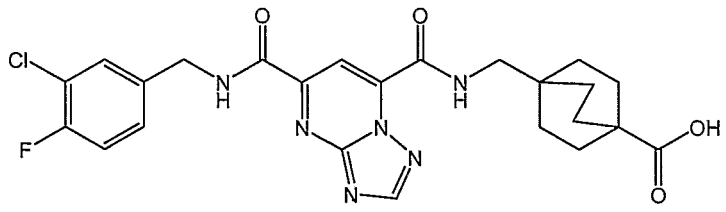
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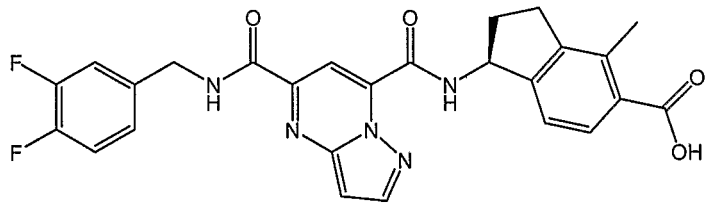
or a pharmaceutically acceptable salt thereof.

96. The compound of claim 18, having the structure:



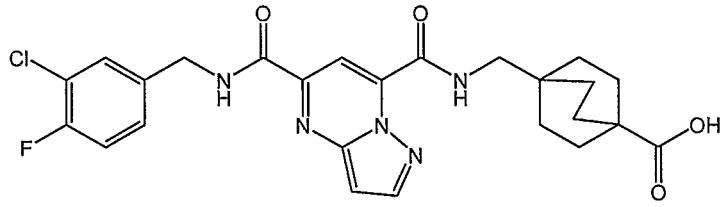
or a pharmaceutically acceptable salt thereof.

97. The compound of claim 1, having the structure:



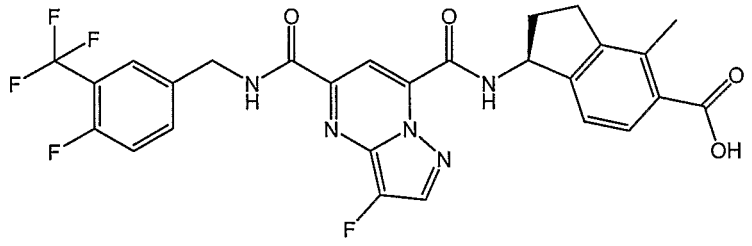
or a pharmaceutically acceptable salt thereof.

98. The compound of claim 18, having the structure:



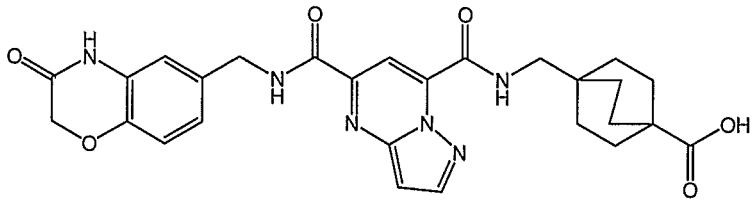
or a pharmaceutically acceptable salt thereof.

99. The compound of claim 1, having the structure:



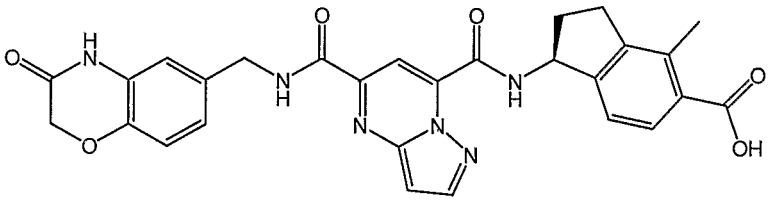
or a pharmaceutically acceptable salt thereof.

100. The compound of claim 18, having the structure:



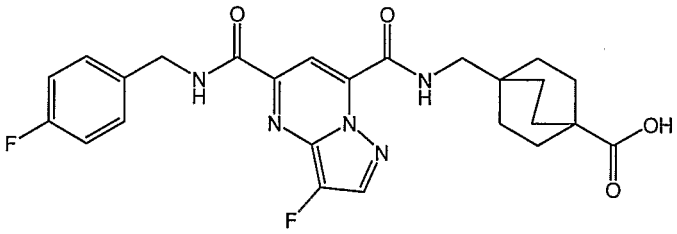
or a pharmaceutically acceptable salt thereof.

101. The compound of claim 1, having the structure:



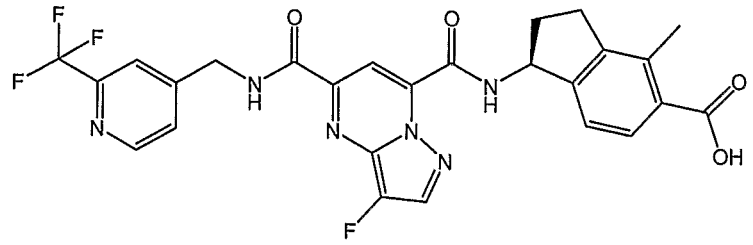
or a pharmaceutically acceptable salt thereof.

102. The compound of claim 18, having the structure:



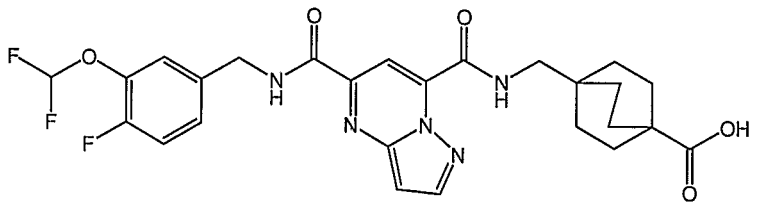
or a pharmaceutically acceptable salt thereof.

103. The compound of claim 1, having the structure:



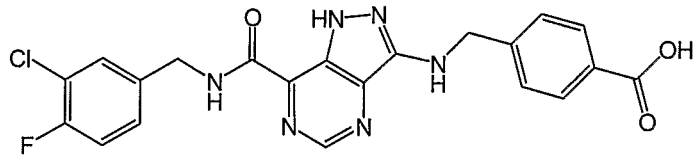
or a pharmaceutically acceptable salt thereof.

104. The compound of claim 18, having the structure:



or a pharmaceutically acceptable salt thereof.

105. The compound of claim 64, having the structure:



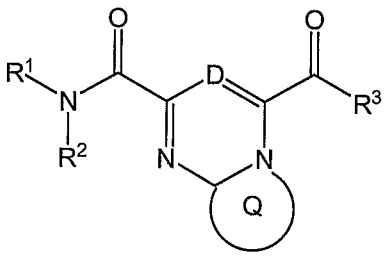
or a pharmaceutically acceptable salt thereof.

106. A pharmaceutical composition comprising an effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

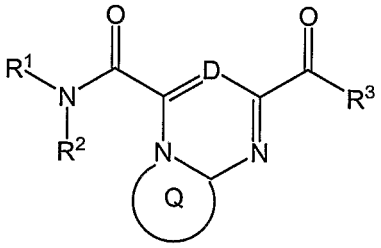
107. A pharmaceutical composition comprising an effective amount of the compound of claim 18 and a pharmaceutically acceptable carrier.

108. A pharmaceutical composition comprising an effective amount of the compound of claim 48, and a pharmaceutically acceptable carrier.

109. A method of inhibiting MMP-13, comprising administering to a subject in need of such treatment a compound selected from the group consisting of: a compound of Formula (I) and a compound of Formula (III):



Formula (I)



Formula (III)

wherein:

R^1 is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl

fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^3 is $NR^{20}R^{21}$;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)\text{-}NR^{11}$-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)\text{-}NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted one or more times, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{20} is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times;

R^{21} is a bicyclic or tricyclic fused ring system, wherein at least one ring is partially saturated, and wherein the bicyclic or tricyclic fused ring system is optionally substituted one or more times;

R^{22} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N{=}CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, SO_2R^{10} , $SO_2NR^{10}R^{11}$ and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{30} is selected from the group consisting of alkyl and $(C_0\text{-}C_6)$-alkyl-aryl, wherein alkyl and aryl are optionally substituted;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted one or more times;

Q is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

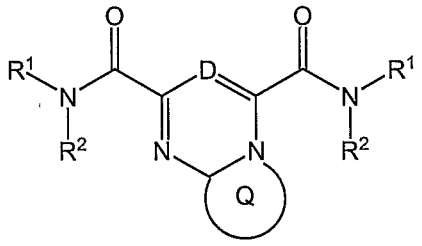
D is a member selected from the group consisting of CR^{22} and N;

x is selected from 0 to 2;

y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

110. A method of inhibiting MMP-13, comprising administering to a subject in need of such treatment a compound of Formula (II):



Formula (II)

wherein:

R^1 is independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl,

spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)\text{-}NR^{11}$-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)\text{-}NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{22} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N{=}CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, SO_2R^{10}, $SO_2NR^{10}R^{11}$ and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted one or more times;

Q is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

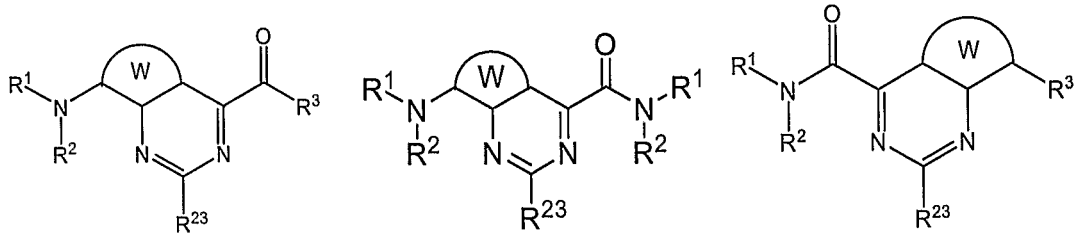
D is a member selected from the group consisting of CR^{22} and N;

x is selected from 0 to 2;

y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

111. A method of inhibiting MMP-13, comprising administering to a subject in need of such treatment a compound selected from the group consisting of: a compound of Formula (IV), a compound of Formula (V), and a compound of Formula (VI):



Formula (IV) Formula (V) Formula (VI)

wherein:

R^1 is independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^3 is $NR^{20}R^{21}$;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-C(O)-NR^{11}-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{20} is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted;

R^{21} is a bicyclic or tricyclic fused ring system, wherein at least one ring is partially saturated, and wherein the bicyclic or tricyclic fused ring system is optionally substituted;

R^{23} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N{=}CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$ are optionally substituted;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted;

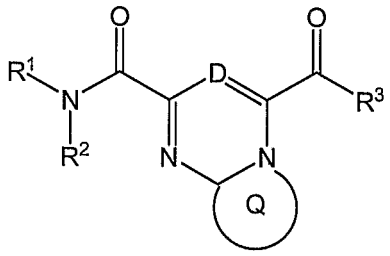
W is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

x is selected from 0 to 2;

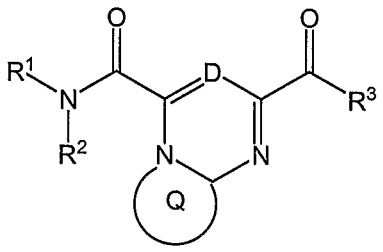
y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

112. A method of treating an MMP-13 mediated disease, comprising administering to a subject in need of such treatment an effective amount of a compound selected from the group consisting of: a compound of Formula (I) and a compound of Formula (III):



Formula (I)



Formula (III)

wherein:

R^1 is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^3 is $NR^{20}R^{21}$;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-C(O)-NR^{11}-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted one or more times, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{20} is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times;

R^{21} is a bicyclic or tricyclic fused ring system, wherein at least one ring is partially saturated, and wherein the bicyclic or tricyclic fused ring system is optionally substituted one or more times;

R^{22} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N{=}CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, SO_2R^{10}, $SO_2NR^{10}R^{11}$ and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{30} is selected from the group consisting of alkyl and $(C_0\text{-}C_6)$-alkyl-aryl, wherein alkyl and aryl are optionally substituted;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted one or more times;

Q is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

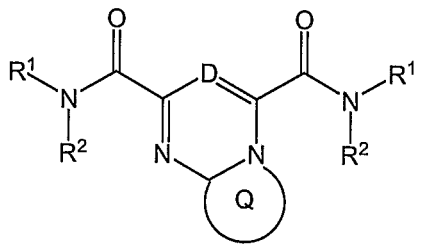
D is a member selected from the group consisting of CR^{22} and N;

x is selected from 0 to 2;

y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

113. A method of treating an MMP-13 mediated disease, comprising administering to a subject in need of such treatment an effective amount of a compound of Formula (II):



Formula (II)

wherein:

R^1 is independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and

optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-C(O)-NR^{11}-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{22} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$,

$NR^{10}N=CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, SO_2R^{10} , $SO_2NR^{10}R^{11}$ and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted one or more times;

Q is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

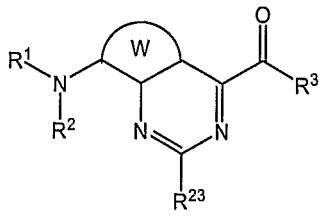
D is a member selected from the group consisting of CR^{22} and N;

x is selected from 0 to 2;

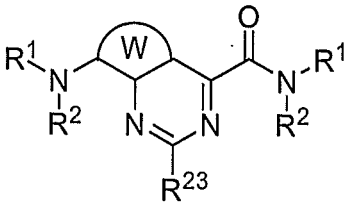
y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

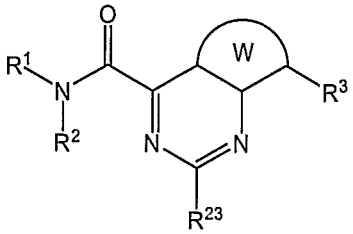
114. A method of treating an MMP-13 mediated disease, comprising administering to a subject in need of such treatment an effective amount of a compound selected from the group consisting of: a compound of Formula (IV), a compound of Formula (V), and a compound of Formula (VI):



Formula (IV)



Formula (V)



Formula (VI)

wherein:

R^1 is independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^3 is $NR^{20}R^{21}$;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0$-$C_6)$-

alkyl-COR^{10}, (C_0-C_6)-alkyl-OR^{10}, (C_0-C_6)-alkyl-$NR^{10}R^{11}$, (C_0-C_6)-alkyl-NO_2, (C_0-C_6)-alkyl-CN, (C_0-C_6)-alkyl-$S(O)_yOR^{10}$, (C_0-C_6)-alkyl-$S(O)_yNR^{10}R^{11}$, (C_0-C_6)-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, ($C_0$-$C_6$)-alkyl-$S(O)_xR^{10}$, ($C_0$-$C_6$)-alkyl-$OC(O)R^{10}$, ($C_0$-$C_6$)-alkyl-$OC(O)NR^{10}R^{11}$, ($C_0$-$C_6$)-alkyl-$C(=NR^{10})NR^{10}R^{11}$, ($C_0$-$C_6$)-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, ($C_0$-$C_6$)-alkyl-$C(O)OR^{10}$, ($C_0$-$C_6$)-alkyl-$C(O)NR^{10}R^{11}$, ($C_0$-$C_6$)-alkyl-$C(O)NR^{10}SO_2R^{11}$, ($C_0$-$C_6$)-alkyl-C(O)-$NR^{11}$-CN, O-($C_0$-$C_6$)-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-(C_0-C_6)-alkyl-$C(O)OR^{10}$, $S(O)_x$-(C_0-C_6)-alkyl-$C(O)NR^{10}R^{11}$, (C_0-C_6)-alkyl-$C(O)NR^{10}$-(C_0-C_6)-alkyl-$NR^{10}R^{11}$, (C_0-C_6)-alkyl-NR^{10}-$C(O)R^{10}$, (C_0-C_6)-alkyl-NR^{10}-$C(O)OR^{10}$, (C_0-C_6)-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, (C_0-C_6)-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, (C_0-C_6)-alkyl-NR^{10}-$S(O)_yR^{10}$, O-(C_0-C_6)-alkyl-aryl and O-(C_0-C_6)-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{20} is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted;

R^{21} is a bicyclic or tricyclic fused ring system, wherein at least one ring is partially saturated, and wherein the bicyclic or tricyclic fused ring system is optionally substituted;

R^{23} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$,

$NR^{10}N=CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$ are optionally substituted;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted;

W is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

x is selected from 0 to 2;

y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

115. The method according to claim 112, wherein the disease is rheumatoid arthritis.

116. The method according to claim 112, wherein the disease is osteoarthritis.

117. The method according to claim 112, wherein the disease is inflammation.

118. The method according to claim 112, wherein the disease is atherosclerosis.

119. The method according to claim 113, wherein the disease is rheumatoid arthritis.

120. The method according to claim 113, wherein the disease is osteoarthritis.

121. The method according to claim 113, wherein the disease is inflammation.

122. The method according to claim 113, wherein the disease is atherosclerosis.

123. The method according to claim 114, wherein the disease is rheumatoid arthritis.

124. The method according to claim 114, wherein the disease is osteoarthritis.

125. The method according to claim 114, wherein the disease is inflammation.

126. The method according to claim 114, wherein the disease is atherosclerosis.

127. The method according to claim 112, wherein the disease is selected from the group consisting of: rheumatoid arthritis, osteoarthritis, abdominal aortic aneurysm, cancer, inflammation, atherosclerosis, multiple sclerosis, chronic obstructive pulmonary disease, ocular diseases, neurologic diseases, psychiatric diseases, thrombosis, bacterial infection, Parkinson's disease, fatigue, tremor, diabetic retinopathy, vascular diseases of the retina, aging, dementia, cardiomyopathy, renal tubular impairment, diabetes, psychosis, dyskinesia, pigmentary abnormalities, deafness, inflammatory and fibrotic syndromes, intestinal bowel syndrome, allergies, Alzheimers disease, arterial plaque formation, oncology, periodontal, viral infection, stroke, atherosclerosis, cardiovascular disease, reperfusion injury, trauma, chemical exposure or oxidative damage to tissues, wound healing, hemorroid, skin beautifying, pain, inflammatory pain, bone pain and joint pain.

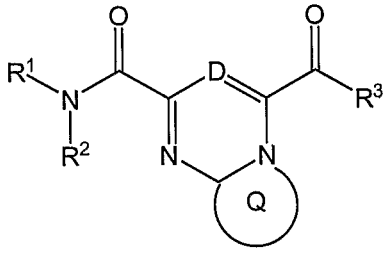
128. The method according to claim 113, wherein the disease is selected from the group consisting of: rheumatoid arthritis, osteoarthritis, abdominal aortic aneurysm, cancer, inflammation, atherosclerosis, multiple sclerosis, chronic obstructive pulmonary disease, ocular diseases, neurologic diseases, psychiatric diseases, thrombosis, bacterial infection, Parkinson's disease, fatigue, tremor, diabetic retinopathy, vascular diseases of the retina, aging, dementia, cardiomyopathy, renal tubular impairment, diabetes, psychosis, dyskinesia, pigmentary abnormalities, deafness, inflammatory and fibrotic syndromes, intestinal bowel syndrome, allergies, Alzheimers disease, arterial plaque formation, oncology, periodontal, viral infection, stroke, atherosclerosis, cardiovascular disease, reperfusion injury, trauma, chemical exposure or oxidative damage to tissues, wound healing, hemorroid, skin beautifying, pain, inflammatory pain, bone pain and joint pain.

129. The method according to claim 114, wherein the disease is selected from the group consisting of: rheumatoid arthritis, osteoarthritis, abdominal aortic aneurysm, cancer, inflammation, atherosclerosis, multiple sclerosis, chronic obstructive pulmonary disease, ocular diseases, neurologic diseases, psychiatric diseases, thrombosis, bacterial infection, Parkinson's disease, fatigue, tremor, diabetic retinopathy, vascular diseases of the retina, aging, dementia, cardiomyopathy, renal tubular impairment, diabetes, psychosis, dyskinesia,

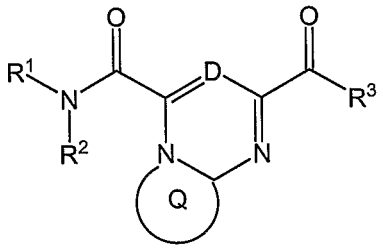
pigmentary abnormalities, deafness, inflammatory and fibrotic syndromes, intestinal bowel syndrome, allergies, Alzheimers disease, arterial plaque formation, oncology, periodontal, viral infection, stroke, atherosclerosis, cardiovascular disease, reperfusion injury, trauma, chemical exposure or oxidative damage to tissues, wound healing, pain, hemorroid, skin beautifying, inflammatory pain, bone pain and joint pain.

130. A pharmaceutical composition comprising:

A) an effective amount of a compound selected from the group consisting of: a compound of Formula (I) and a compound of Formula (III):



Formula (I)



Formula (III)

wherein:

R^1 is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl

fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^3 is $NR^{20}R^{21}$;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-C(O)-NR^{11}-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted one or more times, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{20} is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times;

R^{21} is a bicyclic or tricyclic fused ring system, wherein at least one ring is partially saturated, and wherein the bicyclic or tricyclic fused ring system is optionally substituted one or more times;

R^{22} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N{=}CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, SO_2R^{10}, $SO_2NR^{10}R^{11}$ and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{30} is selected from the group consisting of alkyl and $(C_0\text{-}C_6)$-alkyl-aryl, wherein alkyl and aryl are optionally substituted;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted one or more times;

Q is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

D is a member selected from the group consisting of CR^{22} and N;

x is selected from 0 to 2;

y is selected from 1 and 2;

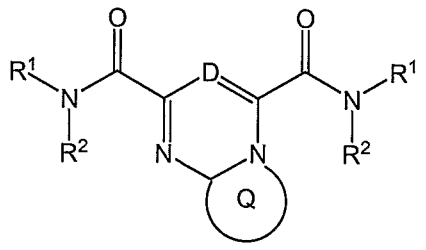
N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof;

B) a pharmaceutically acceptable carrier; and

C) a member selected from the group consisting of: (a) a disease modifying antirheumatic drug; (b) a nonsteroidal anti-inflammatory drug; (c) a COX-2 selective inhibitor; (d) a COX-1 inhibitor; (e) an immunosuppressive; (f) a steroid; (g) a biological response modifier; and (h) a small molecule inhibitor of pro-inflammatory cytokine production.

131. A pharmaceutical composition comprising:

A) an effective amount of a compound according to Formula (II):



Formula (II)

wherein:

R^1 is independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-C(O)-NR^{11}-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{22} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N=CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, SO_2R^{10}, $SO_2NR^{10}R^{11}$ and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted one or more times;

Q is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

D is a member selected from the group consisting of CR^{22} and N;

x is selected from 0 to 2;

y is selected from 1 and 2;

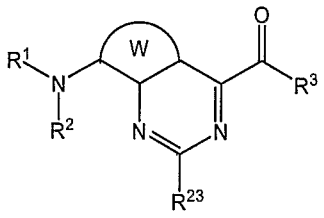
N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof;

B) a pharmaceutically acceptable carrier; and

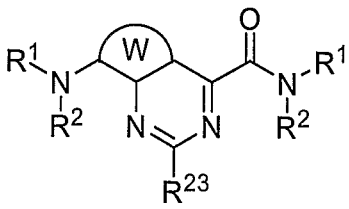
C) a member selected from the group consisting of: (a) a disease modifying antirheumatic drug; (b) a nonsteroidal anti-inflammatory drug; (c) a COX-2 selective inhibitor; (d) a COX-1 inhibitor; (e) an immunosuppressive; (f) a steroid; (g) a biological response modifier; and (h) a small molecule inhibitor of pro-inflammatory cytokine production.

132. A pharmaceutical composition comprising:

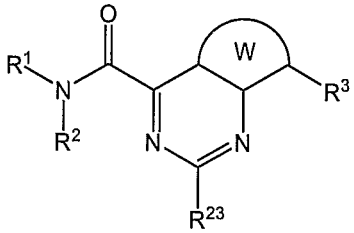
A) an effective amount of a compound selected from the group consisting of a compound of Formula (IV), a compound of Formula (V), and a compound of Formula (VI):



Formula (IV)



Formula (V)



Formula (VI)

wherein:

R^1 is independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^3 is $NR^{20}R^{21}$;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-C(O)-NR^{11}-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0$-

C_6)-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{20} is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted;

R^{21} is a bicyclic or tricyclic fused ring system, wherein at least one ring is partially saturated, and wherein the bicyclic or tricyclic fused ring system is optionally substituted;

R^{23} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N{=}CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$ are optionally substituted;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl,

heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted;

W is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

x is selected from 0 to 2;

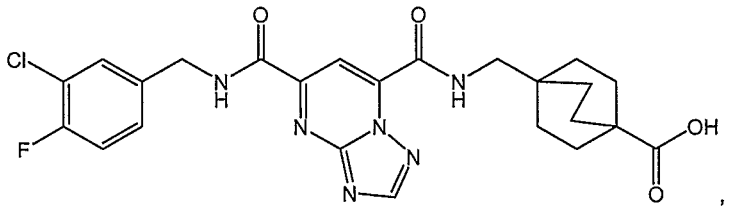
y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof;

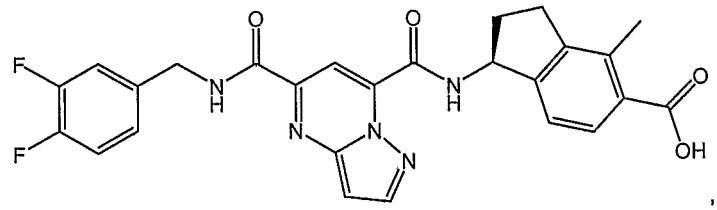
B) a pharmaceutically acceptable carrier; and

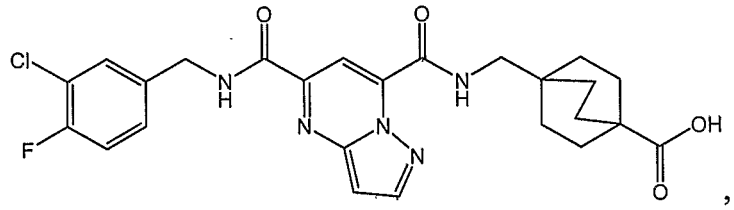
C) a member selected from the group consisting of: (a) a disease modifying antirheumatic drug; (b) a nonsteroidal anti-inflammatory drug; (c) a COX-2 selective inhibitor; (d) a COX-1 inhibitor; (e) an immunosuppressive; (f) a steroid; (g) a biological response modifier; and (h) a small molecule inhibitor of pro-inflammatory cytokine production.

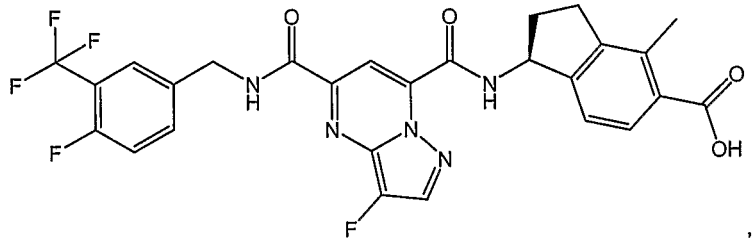
133. A pharmaceutical composition comprising at least one compound selected from the group consisting of:

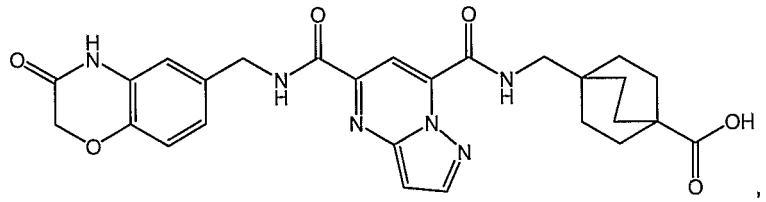


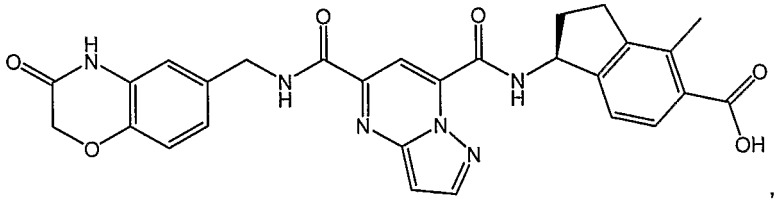
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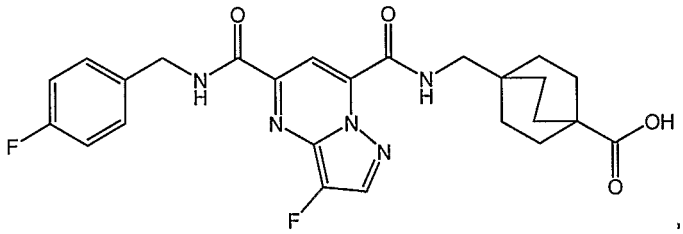


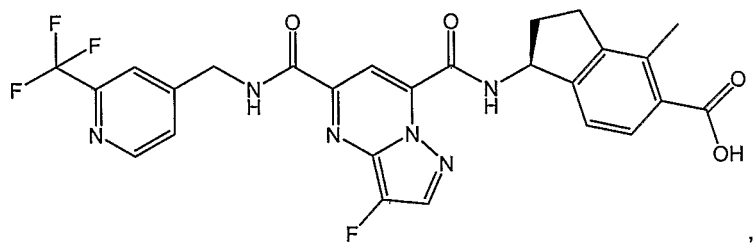


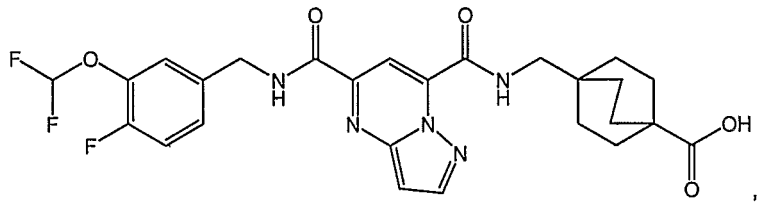




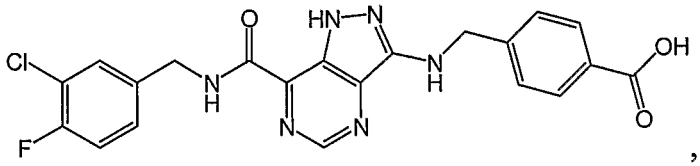








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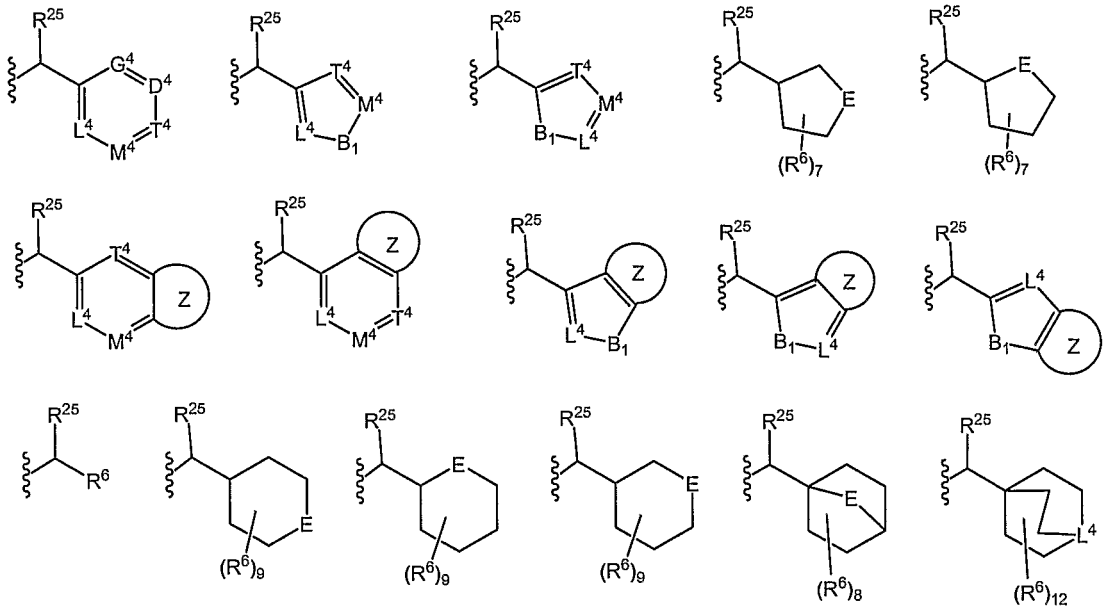


, and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

134. The compound of claim 18, wherein:

A) one R^1 is selected from the group consisting of:



wherein:

R^5 is independently selected from the group consisting of hydrogen, alkyl, $C(O)NR^{10}R^{11}$, aryl, arylalkyl, $SO_2NR^{10}R^{11}$ and $C(O)OR^{10}$ wherein alkyl, aryl and arylalkyl are optionally substituted one or more times;

R^6 is selected from the group consisting of R^9, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $C(O)OR^{10}$, $CH(CH_3)CO_2H$, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$P(O)_2OH$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=N\text{-}CN)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=N\text{-}CN)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=N\text{-}NO_2)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=N\text{-}NO_2)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2NR^{10}$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2NR^{10}$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $S(O)_2NR^{10}$-alkyl, $S(O)_2$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $(C_0\text{-}C_6)$-alkyl-$C(O)\text{-}NR^{11}$-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)\text{-}NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{11}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^6 group is optionally substituted by one or more R^{14} groups;

R^9 is independently selected from the group consisting of hydrogen, alkyl, halo, CHF_2, CF_3, OR^{10}, $NR^{10}R^{11}$, NO_2, and CN, wherein alkyl is optionally substituted one or more times;

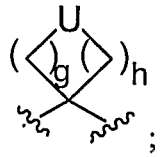
R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $C(O)NR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

R^{30} is selected from the group consisting of alkyl and $(C_0\text{-}C_6)$-alkyl-aryl, wherein alkyl and aryl are optionally substituted;

B_1 is selected from the group consisting of NR^{10}, O and S;

D^4, G^4, L^4, M^4, and T^4 are independently selected from CR^6 or N;

E is selected from the group consisting of a bond, $CR^{10}R^{11}$, O, NR^5, S, S=O, $S(=O)_2$, C(=O), $N(R^{10})(C=O)$, $(C=O)N(R^{10})$, $N(R^{10})S(=O)_2$, $S(=O)_2N(R^{10})$, $C=N\text{-}OR^{11}$, $-C(R^{10}R^{11})C(R^{10}R^{11})-$, $-CH_2\text{-}W^1-$ and



;

W^1 is selected from the group consisting of O, NR^5, S, S=O, $S(=O)_2$, $N(R^{10})(C=O)$, $N(R^{10})S(=O)_2$ and $S(=O)_2N(R^{10})$;

U is selected from $C(R^5R^{10})$, NR^5, O, S, S=O, $S(=O)_2$;

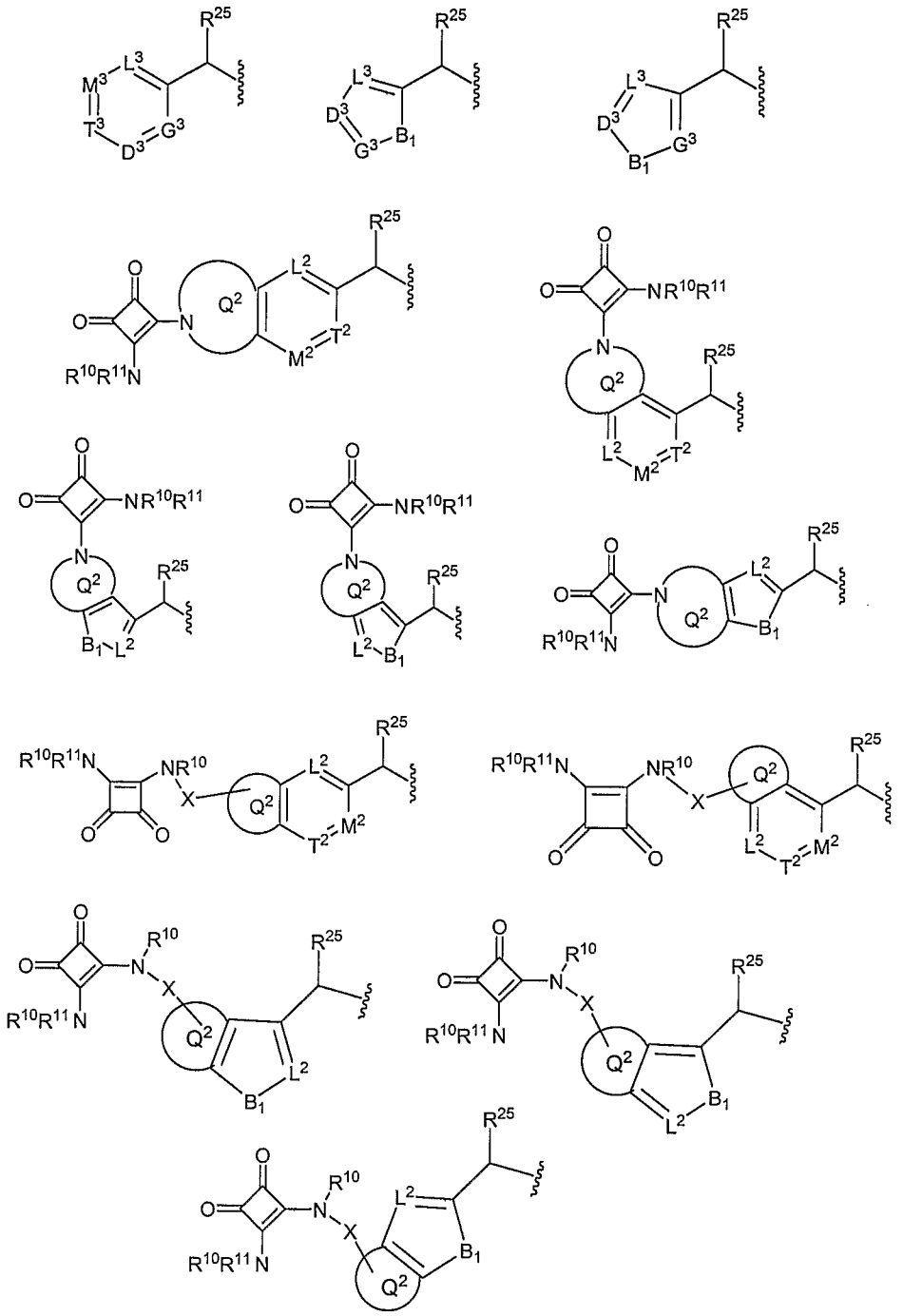
g and h are independently selected from 0-2;

x is selected from 0-2;

y is selected from 1 and 2; and

Z is a 5- to 8-membered ring consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted one ore more times; and

B) one R^1 is selected from the group consisting of:



wherein:

R^5 is independently selected from the group consisting of hydrogen, alkyl, $C(O)NR^{10}R^{11}$, aryl, arylalkyl, $SO_2NR^{10}R^{11}$ and $C(O)OR^{10}$ wherein alkyl, aryl and arylalkyl are optionally substituted one or more times;

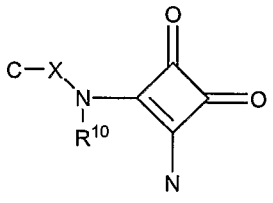
R^{18} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{19} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two R^{19} groups together at one carbon atom form =O, =S or $=NR^{10}$;

R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $CONR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl and haloalkyl are optionally substituted one or more times;

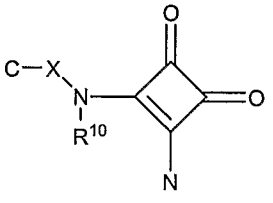
L^2, M^2, and T^2 are independently selected from the group consisting of CR^{18} and N;

L^3, M^3, T^3, D^3, and G^3 are independently selected from N, CR^{18}, and



,

with the provision that one of L^3, M^3, T^3, D^3, and G^3 is

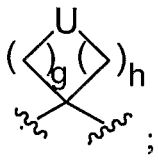


;

B_1 is selected from the group consisting of NR^{10}, O and S;

X is selected from the group consisting of a bond and $(CR^{10}R^{11})_wE(CR^{10}R^{11})_w$

E is selected from the group consisting of a bond, $CR^{10}R^{11}$, O, NR^5, S, S=O, $S(=O)_2$, C(=O), $N(R^{10})(C=O)$, $(C=O)N(R^{10})$, $N(R^{10})S(=O)_2$, $S(=O)_2N(R^{10})$, C=N-OR^{11}, $-C(R^{10}R^{11})C(R^{10}R^{11})-$, $-CH_2-W^1-$ and



;

W^1 is selected from the group consisting of O, NR^5, S, S=O, $S(=O)_2$, $N(R^{10})(C=O)$, $N(R^{10})S(=O)_2$ and $S(=O)_2N(R^{10})$;

U is selected from $C(R^5R^{10})$, NR^5, O, S, S=O, $S(=O)_2$;

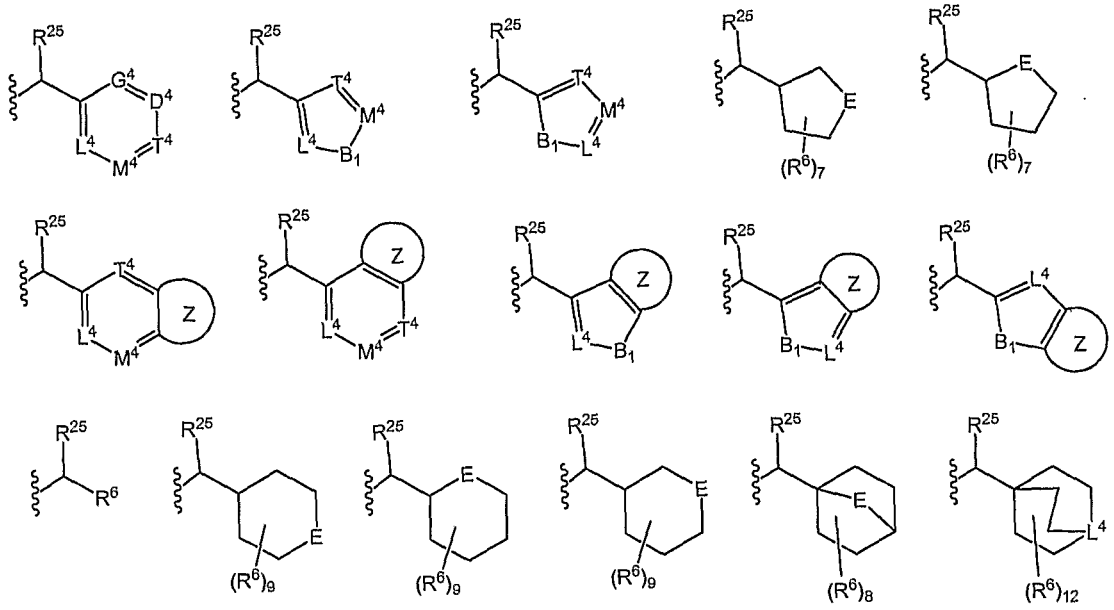
g and h are independently selected from 0-2;

w is selected from 0-4; and

Q^2 is a 5- to 8-membered ring consisting of cycloalkyl, heterocycloalkyl, aryl, heteroaryl, which is optionally substituted one or more times with R^{19}.

135. The compound of claim 64, wherein:

A) one R^1 is selected from the group consisting of:



wherein:

R^5 is independently selected from the group consisting of hydrogen, alkyl, $C(O)NR^{10}R^{11}$, aryl, arylalkyl, $SO_2NR^{10}R^{11}$ and $C(O)OR^{10}$ wherein alkyl, aryl and arylalkyl are optionally substituted one or more times;

R^6 is selected from the group consisting of R^9, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $C(O)OR^{10}$, $CH(CH_3)CO_2H$, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$P(O)_2OH$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=N\text{-}CN)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=N\text{-}CN)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=N\text{-}NO_2)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=N\text{-}NO_2)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2NR^{10}$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2NR^{10}$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $S(O)_2NR^{10}$-alkyl, $S(O)_2$-$(C_0\text{-}C_6)$-alkyl-aryl, $S(O)_2$-$(C_0\text{-}C_6)$-alkyl-heteroaryl, $(C_0\text{-}C_6)$-alkyl-$C(O)\text{-}NR^{11}$-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}\text{-}C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}\text{-}C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}\text{-}C(O)\text{-}NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-

$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{11}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^6 group is optionally substituted by one or more R^{14} groups;

R^9 is independently selected from the group consisting of hydrogen, alkyl, halo, CHF_2, CF_3, OR^{10}, $NR^{10}R^{11}$, NO_2, and CN, wherein alkyl is optionally substituted one or more times;

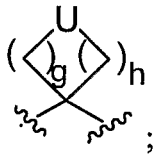
R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $C(O)NR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl, and haloalkyl are optionally substituted one or more times;

R^{30} is selected from the group consisting of alkyl and $(C_0\text{-}C_6)$-alkyl-aryl, wherein alkyl and aryl are optionally substituted;

B_1 is selected from the group consisting of NR^{10}, O and S;

D^4, G^4, L^4, M^4, and T^4, are independently selected from CR^6 or N;

E is selected from the group consisting of a bond, $CR^{10}R^{11}$, O, NR^5, S, S=O, $S(=O)_2$, C(=O), $N(R^{10})(C=O)$, $(C=O)N(R^{10})$, $N(R^{10})S(=O)_2$, $S(=O)_2N(R^{10})$, C=N-OR^{11}, $-C(R^{10}R^{11})C(R^{10}R^{11})-$, $-CH_2-W^1-$ and



;

W^1 is selected from the group consisting of O, NR^5, S, S=O, $S(=O)_2$, $N(R^{10})(C=O)$, $N(R^{10})S(=O)_2$ and $S(=O)_2N(R^{10})$;

U is selected from $C(R^5R^{10})$, NR^5, O, S, S=O, $S(=O)_2$;

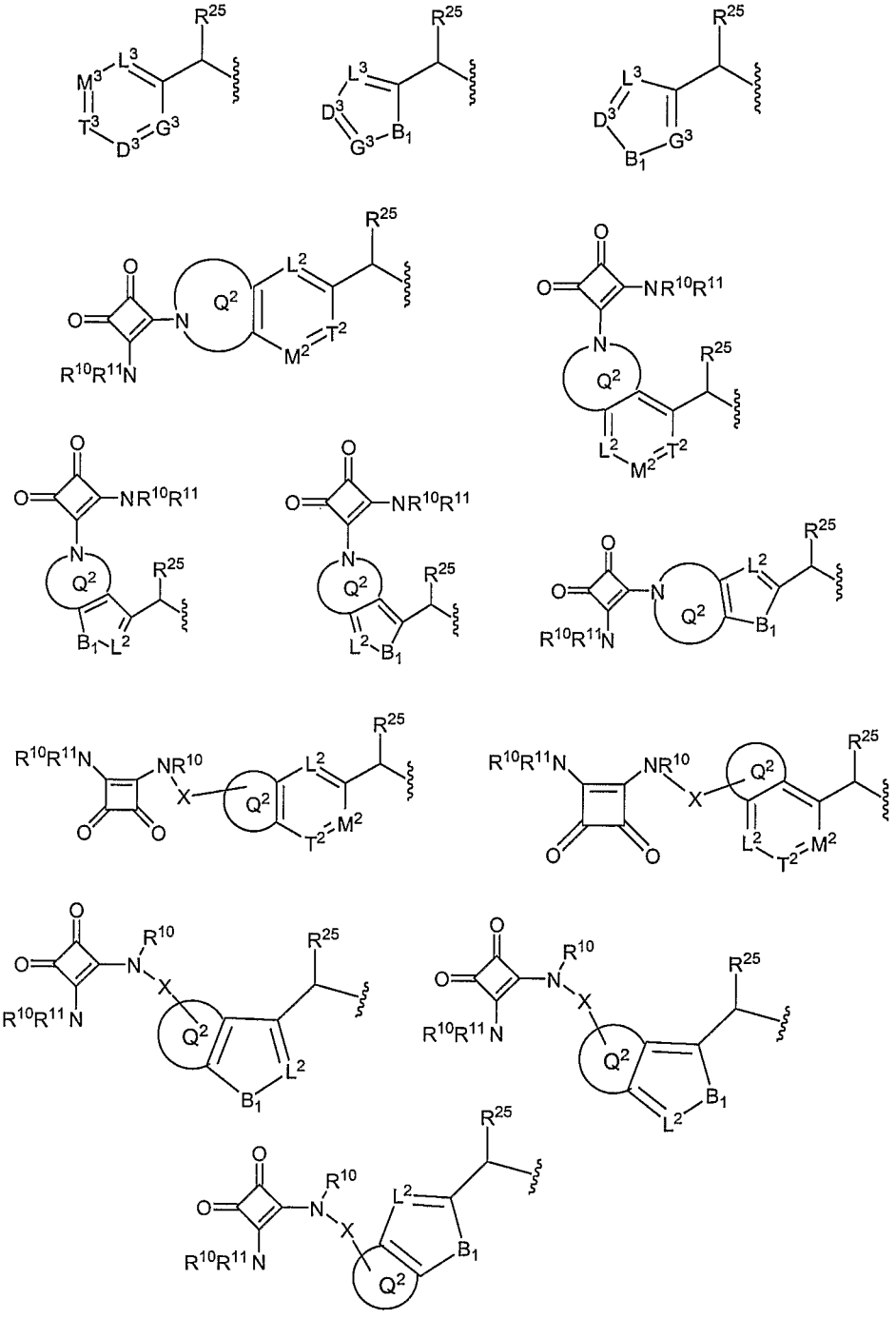
g and h are independently selected from 0-2;

p is selected from 0-6;

y is selected from 1 and 2; and

Z is a 5- to 8-membered ring consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are optionally substituted one ore more times; and

B) one R^1 is selected from the group consisting of:



wherein:

R^5 is independently selected from the group consisting of hydrogen, alkyl, $C(O)NR^{10}R^{11}$, aryl, arylalkyl, $SO_2NR^{10}R^{11}$ and $C(O)OR^{10}$ wherein alkyl, aryl and arylalkyl are optionally substituted one or more times;

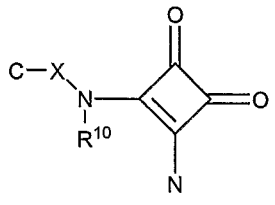
R^{18} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{19} is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, heteroaryl, OH, halo, CN, $C(O)NR^{10}R^{11}$, CO_2R^{10}, OR^{10}, OCF_3, $OCHF_2$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}COR^{11}$, $NR^{10}SO_2R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$ and $NR^{10}R^{11}$, wherein alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, alkynyl, aryl, and heteroaryl are optionally substituted one or more times, or optionally two R^{19} groups together at one carbon atom form =O, =S or $=NR^{10}$;

R^{25} is selected from the group consisting of hydrogen, alkyl, cycloalkyl, $CONR^{10}R^{11}$ and haloalkyl, wherein alkyl, cycloalkyl and haloalkyl are optionally substituted one or more times;

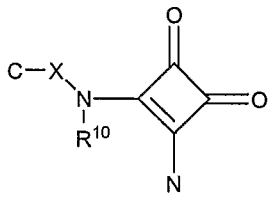
L^2, M^2, and T^2 are independently selected from the group consisting of CR^{18} and N;

L^3, M^3, T^3, D^3, and G^3 are independently selected from N, CR^{18}, and



,

with the provision that one of L^3, M^3, T^3, D^3, and G^3 is

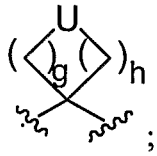


;

B_1 is selected from the group consisting of NR^{10}, O and S;

X is selected from the group consisting of a bond and $(CR^{10}R^{11})_wE(CR^{10}R^{11})_w$

E is selected from the group consisting of a bond, $CR^{10}R^{11}$, O, NR^5, S, S=O, $S(=O)_2$, C(=O), $N(R^{10})(C=O)$, $(C=O)N(R^{10})$, $N(R^{10})S(=O)_2$, $S(=O)_2N(R^{10})$, $C=N\text{-}OR^{11}$, $-C(R^{10}R^{11})C(R^{10}R^{11})-$, $-CH_2\text{-}W^1-$ and



;

W^1 is selected from the group consisting of O, NR^5, S, S=O, $S(=O)_2$, $N(R^{10})(C=O)$, $N(R^{10})S(=O)_2$ and $S(=O)_2N(R^{10})$;

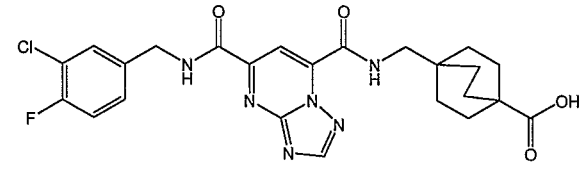
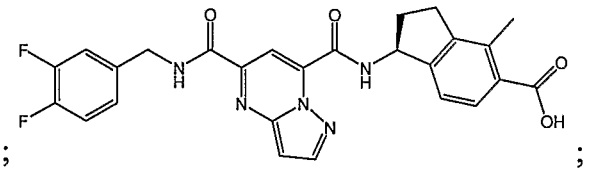
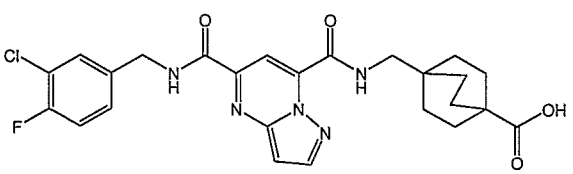
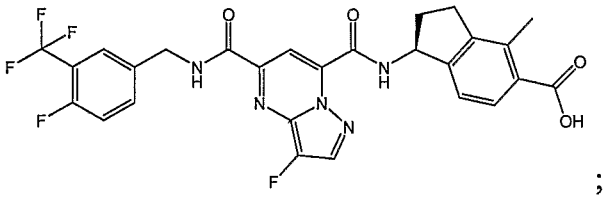
U is selected from $C(R^5R^{10})$, NR^5, O, S, S=O, $S(=O)_2$;

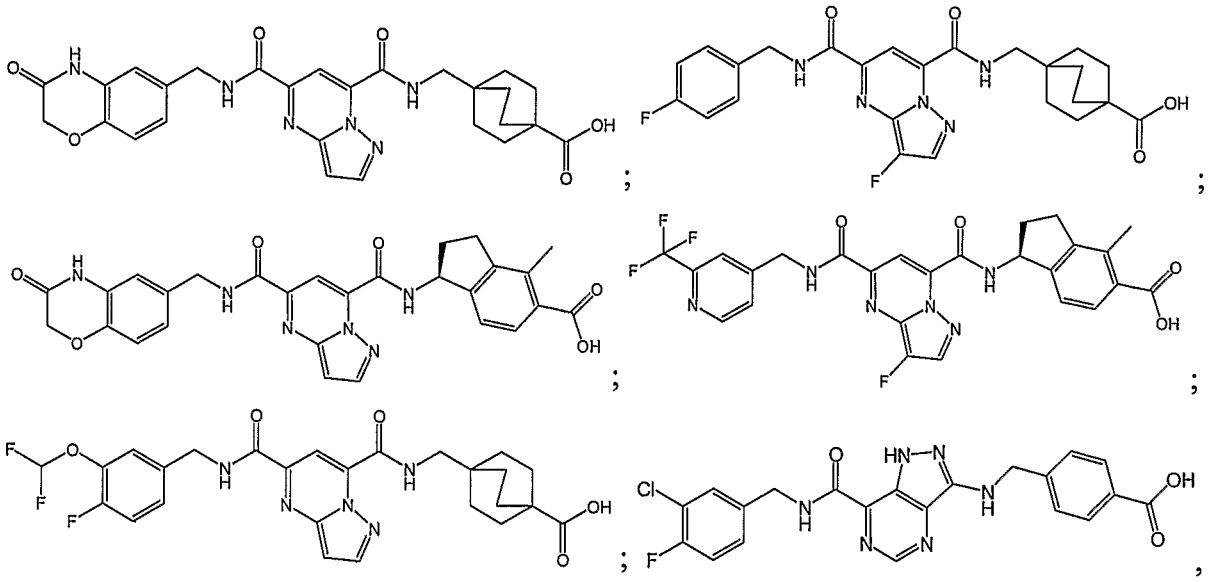
g and h are independently selected from 0-2;

w is selected from 0-4; and

Q^2 is a 5- to 8-membered ring consisting of cycloalkyl, heterocycloalkyl, aryl, heteroaryl, which is optionally substituted one or more times with R^{19}.

136. Use of a compound for the manufacture of a medicament for treating an MMP-13 mediated disease, the compound selected from the group consisting of:

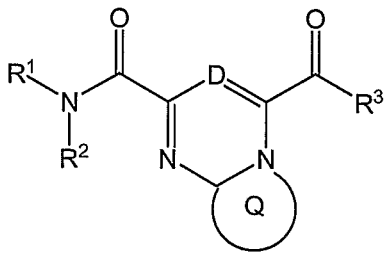

;

;

;

;



and N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof;

and a pharmaceutically acceptable carrier and a drug, agent or therapeutic selected from the group consisting of: (a) a disease modifying antirheumatic drug; (b) a nonsteroidal anti-inflammatory drug e; (c) a COX-2 selective inhibitor; (e) an immunosuppressive; (f) a steroid; (g) a biological response modifier; and (h) a small molecule inhibitor of pro-inflammatory cytokine production.

137. Use of a compound of Formula (I) for the manufacture of a medicament for treating an MMP-13 mediated disease:



Formula (I)

wherein:

R^1 is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^3 is $NR^{20}R^{21}$;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-C(O)-NR^{11}-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0$-

C_6)-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted one or more times, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkyl-alkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkyl-alkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{20} is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times;

R^{21} is a bicyclic or tricyclic fused ring system, wherein at least one ring is partially saturated, and wherein the bicyclic or tricyclic fused ring system is optionally substituted one or more times;

R^{22} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N{=}CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, SO_2R^{10} , $SO_2NR^{10}R^{11}$ and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{30} is selected from the group consisting of alkyl and (C_0-C_6)-alkyl-aryl, wherein alkyl and aryl are optionally substituted;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted one or more times;

Q is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

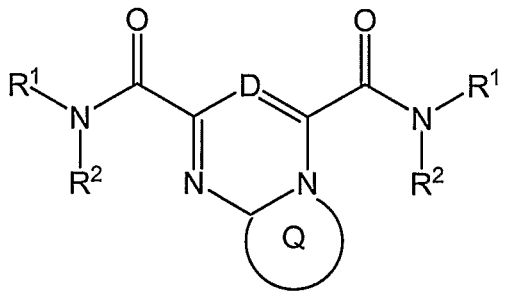
D is a member selected from the group consisting of CR^{22} and N;

x is selected from 0 to 2;

y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof in the manufacture of a medicament for the treatment of a disease mediated by an MMP-13 enzyme.

138. Use of a compound of Formula (II), for the manufacture of a medicament for the treatment of a disease mediated by an MMP-13 enzyme:



Formula (II)

wherein:

R^1 in each occurrence is independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-

$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)\text{-}NR^{11}\text{-}CN$, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)\text{-}NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{22} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N=CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, SO_2R^{10}, $SO_2NR^{10}R^{11}$ and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted one or more times;

Q is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

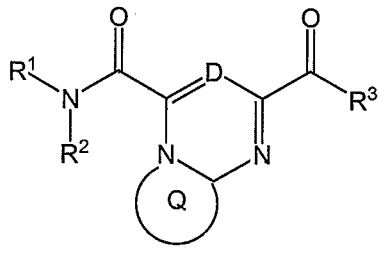
D is a member selected from the group consisting of CR^{22} and N;

x is selected from 0 to 2;

y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

139. Use of a compound of Formula (III), for the manufacture of a medicament for the treatment of a disease mediated by an MMP-13 enzyme:



Formula (III)

wherein:

R^1 is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^3 is $NR^{20}R^{21}$;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-C(O)-NR^{11}-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0$-

C_6)-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted one or more times, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{20} is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times;

R^{21} is a bicyclic or tricyclic fused ring system, wherein at least one ring is partially saturated, and wherein the bicyclic or tricyclic fused ring system is optionally substituted one or more times;

R^{22} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N{=}CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, $C(O)NR^{10}R^{11}$, SO_2R^{10} , $SO_2NR^{10}R^{11}$ and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{30} is selected from the group consisting of alkyl and (C_0-C_6)-alkyl-aryl, wherein alkyl and aryl are optionally substituted;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, and heteroaryl are optionally substituted one or more times;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted one or more times;

Q is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

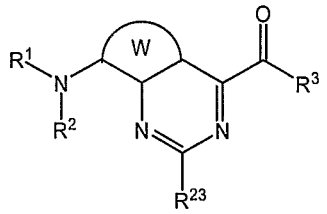
D is a member selected from the group consisting of CR^{22} and N;

x is selected from 0 to 2;

y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

140. Use of a compound of Formula (IV), for the manufacture of a medicament for the treatment of a disease mediated by an MMP-13 enzyme:



Formula (IV)

wherein:

R^1 is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^3 is $NR^{20}R^{21}$;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-C(O)-NR^{11}-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-

alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, (C_0-C_6)-alkyl-NR^{10}-$S(O)_yR^{10}$, O-(C_0-C_6)-alkyl-aryl and O-(C_0-C_6)-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{20} is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted;

R^{21} is a bicyclic or tricyclic fused ring system, wherein at least one ring is partially saturated, and wherein the bicyclic or tricyclic fused ring system is optionally substituted;

R^{23} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N{=}CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{30} is selected from the group consisting of alkyl and (C_0-C_6)-alkyl-aryl, wherein alkyl and aryl are optionally substituted;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein

alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$ are optionally substituted;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted;

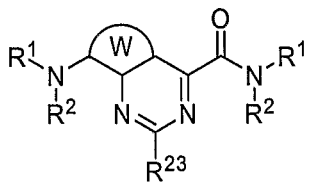
W is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

x is selected from 0 to 2;

y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

141. Use of a compound of Formula (V), for the manufacture of a medicament for the treatment of a disease mediated by an MMP-13 enzyme:



Formula (V)

wherein:

R^1 in each occurrence is independently selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-C(O)-NR^{11}-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{23} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N{=}CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$ are optionally substituted;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted;

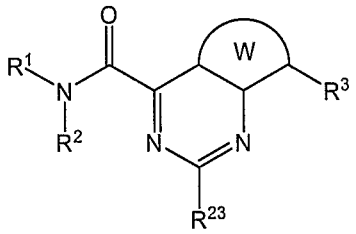
W is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

x is selected from 0 to 2;

y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.

142. Use of a compound of Formula (VI), for the manufacture of a medicament for the treatment of a disease mediated by an MMP-13 enzyme:



Formula (VI)

wherein:

R^1 is selected from the group consisting of alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl, wherein alkyl, cycloalkyl, heterocycloalkyl, bicycloalkyl, heterobicycloalkyl, spiroalkyl, spiroheteroalkyl, aryl, heteroaryl, cycloalkyl fused aryl, heterocycloalkyl fused aryl, cycloalkyl fused heteroaryl, heterocycloalkyl fused heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, bicycloalkylalkyl, heterobicycloalkylalkyl, spiroalkylalkyl, spiroheteroalkylalkyl, arylalkyl, heteroarylalkyl, cycloalkyl fused arylalkyl, heterocycloalkyl

fused arylalkyl, cycloalkyl fused heteroarylalkyl, and heterocycloalkyl fused heteroarylalkyl are optionally substituted one or more times;

R^2 is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted one or more times or R^1 and R^2 when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted one or more times;

R^3 is $NR^{20}R^{21}$;

R^4 in each occurrence is independently selected from the group consisting of R^{10}, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halo, haloalkyl, CF_3, $(C_0\text{-}C_6)$-alkyl-COR^{10}, $(C_0\text{-}C_6)$-alkyl-OR^{10}, $(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NO_2, $(C_0\text{-}C_6)$-alkyl-CN, $(C_0\text{-}C_6)$-alkyl-$S(O)_yOR^{10}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}CONR^{11}SO_2R^{30}$, $(C_0\text{-}C_6)$-alkyl-$S(O)_xR^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-$OC(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(=NR^{10})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$NR^{10}C(=NR^{11})NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}SO_2R^{11}$, $(C_0\text{-}C_6)$-alkyl-C(O)-NR^{11}-CN, O-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)OR^{10}$, $S(O)_x$-$(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-$C(O)NR^{10}$-$(C_0\text{-}C_6)$-alkyl-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)R^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$C(O)OR^{10}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-C(O)-$NR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yNR^{10}R^{11}$, $(C_0\text{-}C_6)$-alkyl-NR^{10}-$S(O)_yR^{10}$, O-$(C_0\text{-}C_6)$-alkyl-aryl and O-$(C_0\text{-}C_6)$-alkyl-heteroaryl, wherein each R^4 group is optionally substituted by one or more R^{14} groups;

R^{10} and R^{11} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{10} and R^{11} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally containing a heteroatom selected from O, $S(O)_x$, or NR^{50} and which is optionally substituted;

R^{14} is independently selected from the group consisting of hydrogen, alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl and halo, wherein alkyl, arylalkyl, cycloalkylalkyl, heteroarylalkyl and heterocyclylalkyl are optionally substituted one or more times.

R^{20} is selected from the group consisting of hydrogen and alkyl, wherein alkyl is optionally substituted;

R^{21} is a bicyclic or tricyclic fused ring system, wherein at least one ring is partially saturated, and wherein the bicyclic or tricyclic fused ring system is optionally substituted;

R^{23} is selected from the group consisting of hydrogen, hydroxy, halo, alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, NO_2, $NR^{10}R^{11}$, CN, SR^{10}, SSR^{10}, PO_3R^{10}, $NR^{10}NR^{10}R^{11}$, $NR^{10}N=CR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, $C(O)OR^{10}$, and fluoroalkyl, wherein alkyl, cycloalkyl, alkoxy, alkenyl, alkynyl, and fluoroalkyl are optionally substituted one or more times;

R^{50} in each occurrence is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$, wherein alkyl, aryl, heteroaryl, $C(O)R^{80}$, $C(O)NR^{80}R^{81}$, SO_2R^{80} and $SO_2NR^{80}R^{81}$ are optionally substituted;

R^{80} and R^{81} in each occurrence are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, haloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl are optionally substituted, or R^{80} and R^{81} when taken together with the nitrogen to which they are attached complete a 3- to 8-membered ring containing carbon atoms and optionally a heteroatom selected from O, $S(O)_x$, -NH, and -N(alkyl) and which is optionally substituted;

W is a 5- or 6-membered ring selected from the group consisting of aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted one or more times with R^4;

x is selected from 0 to 2;

y is selected from 1 and 2; and

N-oxides, pharmaceutically acceptable salts, prodrugs, formulation, polymorphs, racemic mixtures and stereoisomers thereof.