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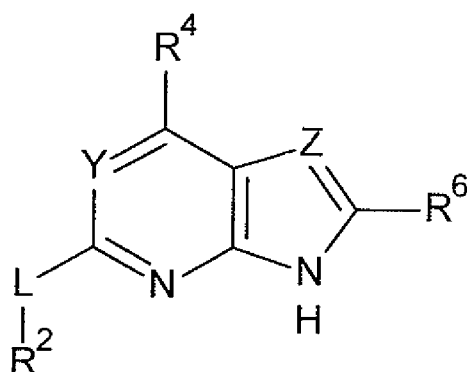
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(54) Title: GYRASE INHIBITORS



(I)

(57) Abstract: Novel gyrase inhibitors and related compositions and methods are useful for impeding bacterial growth. Compounds of Formula (I), are disclosed: Formula (I), wherein Y is N or CH; Z is N or CR⁵; R⁵ is H, a substituted or unsubstituted hydrocarbyl residue (1-3C) containing 0-2 heteroatoms selected from O, S and N, or is an inorganic residue; L is O, S, NR⁷, or CR⁸R⁹; R⁷ is H or C₁₋₃ alkyl; R⁸ and R⁹ are each independently H or C₁₋₃ alkyl; R² is H, a hydrocarbyl residue (1-40C) containing 0-10 heteroatoms selected from O, S and N optionally substituted with an inorganic residue; R⁴ is H, an inorganic residue, or a hydrocarbyl residue (1-30C) containing 0-12 heteroatoms selected from O, S and N and containing 0-10 inorganic residues, wherein R⁵ and R⁴ together may join to form a fused ring; and R⁶ is selected from the group consisting of H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, halo C₁₋₅ alkyl, halo C₂₋₅ alkenyl, halo C₂₋₅ alkynyl, C₁₋₅ hydroxyalkyl, C₁₋₅ alkyl chloride, C₂₋₅ alkenyl chloride, and C₂₋₅ alkynyl chloride; or a pharmaceutically-acceptable salt, ester, or prodrug thereof.

GYRASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to US Provisional Application No. 61/241,833, filed September 11, 2009, which is incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED R&D

[0002] This invention was made with government support under HHSN 272200800042C awarded by the National Institute of Allergy and Infectious Diseases. The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

Field of the Invention

[0003] The disclosure relates to pharmaceutically-useful compositions, methods of making and using them for treatment and prophylaxis of diseases in mammals.

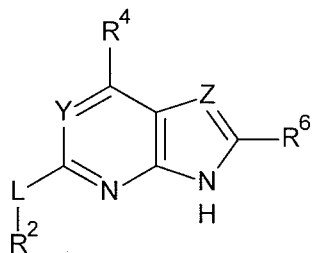
Description of the Related Art

[0004] Bacterial infections pose a continuing medical problem because anti-bacterial drugs eventually engender resistance in the bacteria on which they are used. Consequently, a need exists for new drugs with efficacy against pathogenic bacteria for use in the therapy and prophylaxis of bacterial infections.

[0005] One target for development of anti-bacterial drugs has been topoisomerase gyrase B, an enzyme catalyzes interconversion of topomers of DNA between supercoiled and relaxed forms used for storage and cell division, respectively. Gyrase inhibitors have been disclosed in RE40,245 which is hereby incorporated by reference in its entirety.

SUMMARY OF THE EMBODIMENTS

[0006] A compound useful in pharmaceutical compositions such as antibacterial drugs may have the structure of Formula I:



wherein

Y is N or CH,

Z is N or CR⁵;

R⁵ is H, a substituted or unsubstituted hydrocarbyl residue (1-3C) containing 0-2 heteroatoms selected from O, S and N, or is an inorganic residue;

L is O, S, NR⁷, or CR⁸R⁹;

R⁷ is H or C₁₋₃ alkyl;

R⁸ and R⁹ are each independently H or C₁₋₃ alkyl;

R² is H, a hydrocarbyl residue (1-40C) containing 0-10 heteroatoms selected from O, S and N optionally substituted with an inorganic residue;

R⁴ is H, an inorganic residue, or a hydrocarbyl residue (1-30C) containing 0-12 heteroatoms selected from O, S and N and containing 0-10 inorganic residues, wherein R⁵ and R⁴ together may join to form a fused ring; and

R⁶ is selected from the group consisting of H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, halo C₁₋₅ alkyl, halo C₂₋₅ alkenyl, halo C₂₋₅ alkynyl, C₁₋₅ hydroxyalkyl, C₁₋₅ alkyl chloride, C₂₋₅ alkenyl chloride, and C₂₋₅ alkynyl chloride;

or a pharmaceutically-acceptable salt, ester, or prodrug thereof.

[0007] Some embodiments also include methods of preparing the compound, dosage form or the pharmaceutical composition described herein.

[0008] Embodiments also include methods of and uses for treating a bacterial infection comprising administering the compound, dosage form or the pharmaceutical composition described herein to a subject in need thereof.

[0009] These and other embodiments are described in greater detail below.

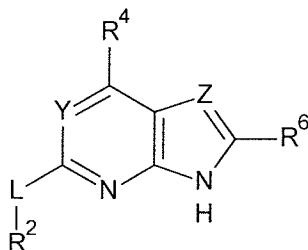
BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Table 1 contains a list of compounds that have been prepared and may be used in pharmaceutical compositions and methods described herein.

[0011] Table 2 lists MIC data for various compounds described herein.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

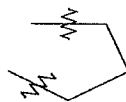
[0012] Compounds herein may have the structure of Formula I:



Y may be N or CH. In some aspects, Y is N.

[0013] Z may be N or CR⁵. R⁵ may be H, a substituted or unsubstituted hydrocarbyl residue (1-3C) containing 0-2 heteroatoms selected from O, S and N, or is an inorganic residue. In some aspects, Z is CR⁵, wherein R⁵ is selected from the group consisting of hydrogen, halo, unsubstituted C₁₋₃ alkyl, or C₁₋₃ alkyl substituted with one or more substituents selected from the group consisting of =O, halo, NH₂, NHCH₃, and ≡N, or C₂₋₃ alkenyl, wherein R⁵ and R⁴ together may join to form a fused ring. For instance, R⁵ may be methyl, C(O)CH₃, C(O)NH₂, CH₂OH, CF₃, CN, CHF₂, CHO, acetyl, Cl or Br.

R⁵ and R⁴ together may form

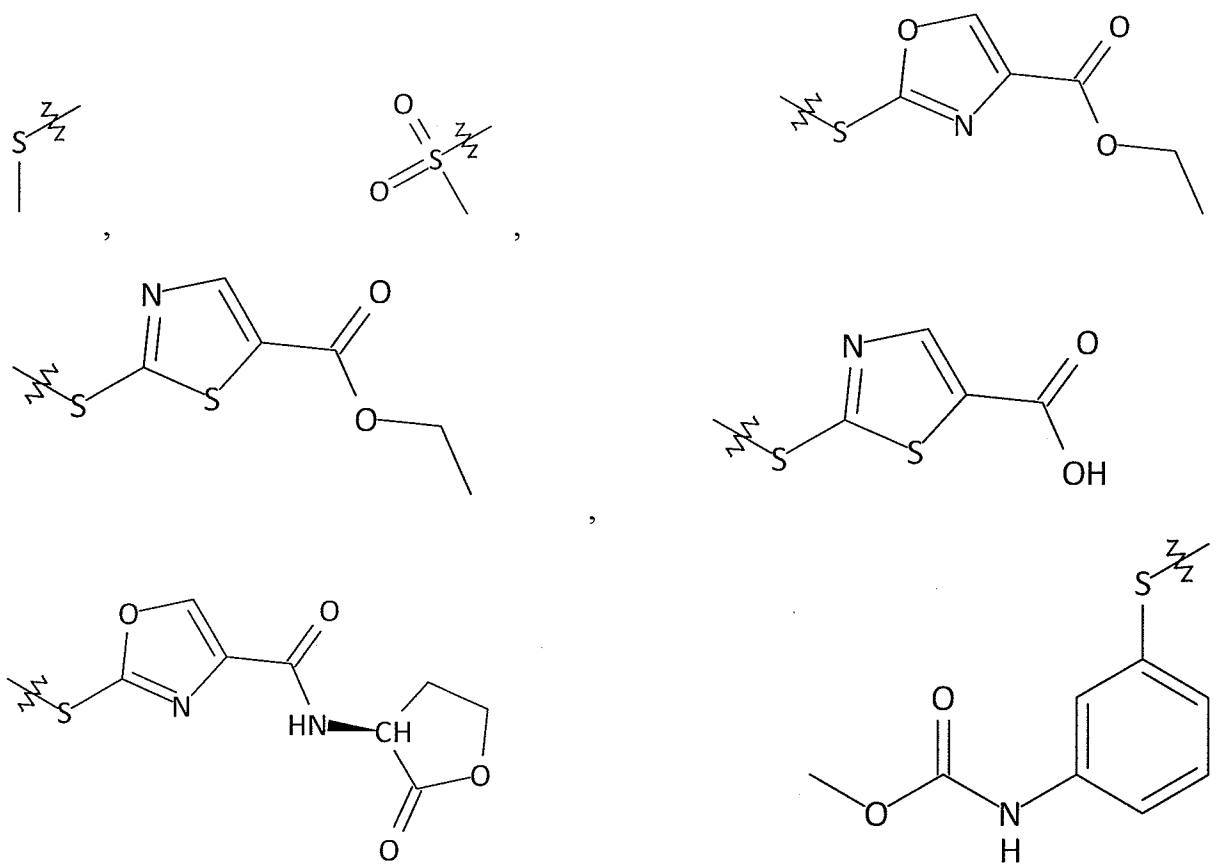


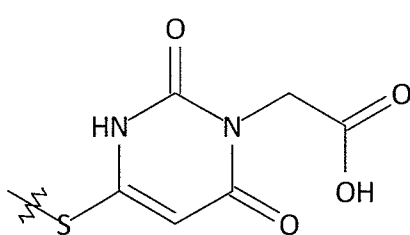
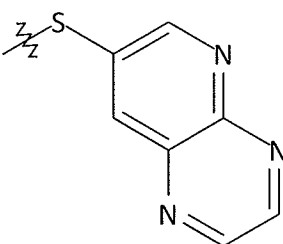
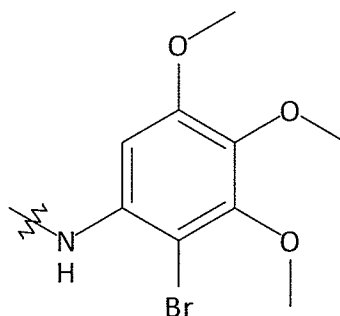
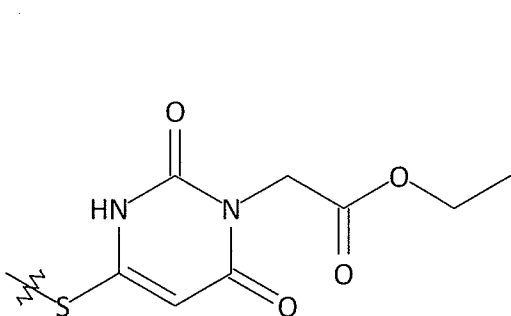
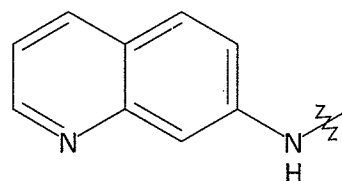
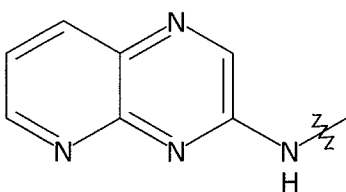
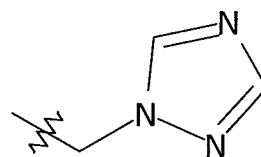
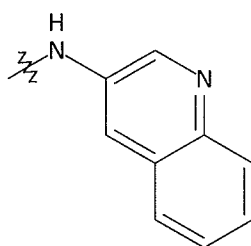
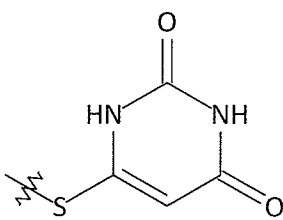
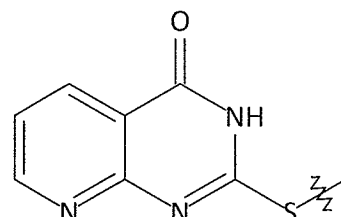
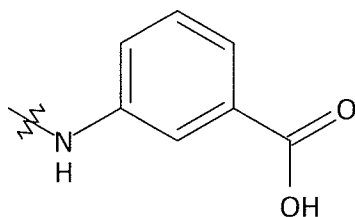
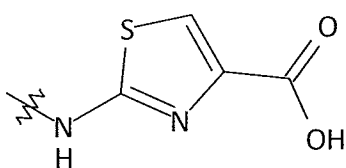
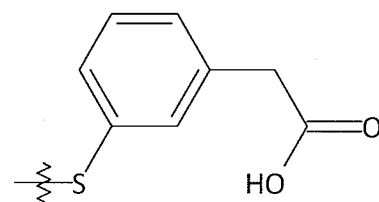
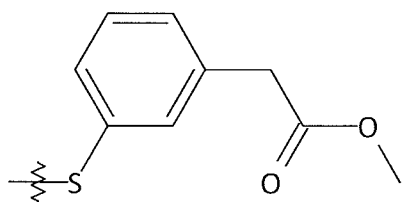
[0014] L is a linker and is intended to impart a distance between portions of the molecule. Typical linkers include O, S, NR⁷, or CR⁸R⁹; wherein R⁷ may be H or C₁₋₃ alkyl and R⁸ and R⁹ may be each independently H or C₁₋₃ alkyl. In some aspects, at least one of R⁸ and R⁹ is H. In some aspects, L may be O, S, NH, or CH₂.

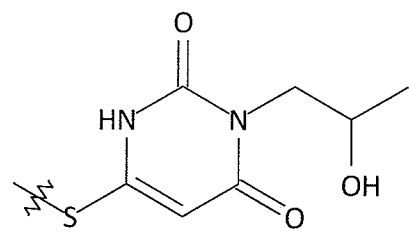
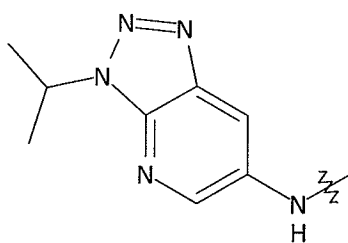
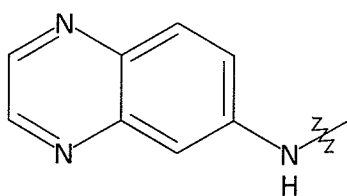
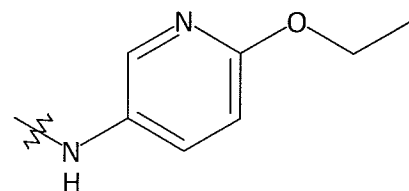
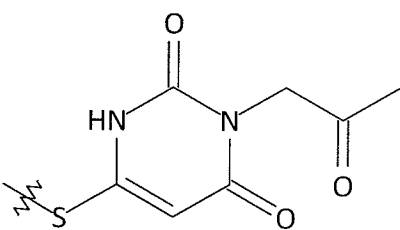
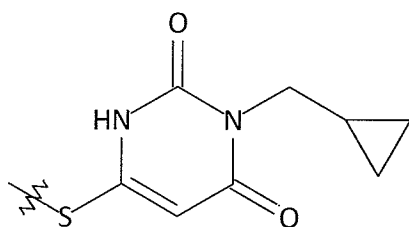
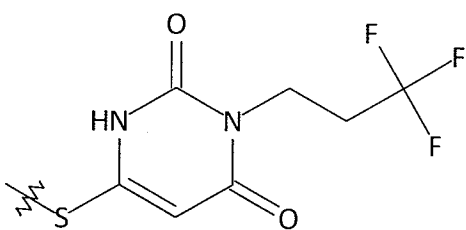
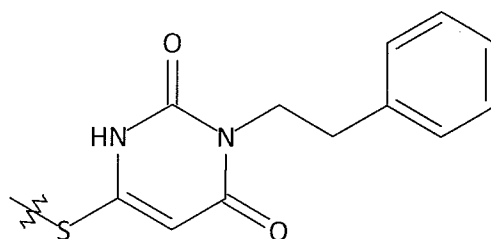
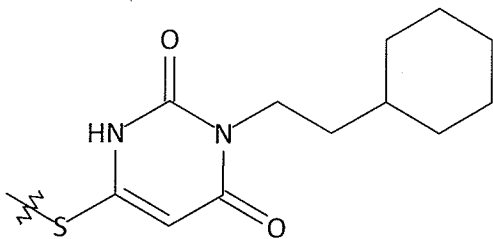
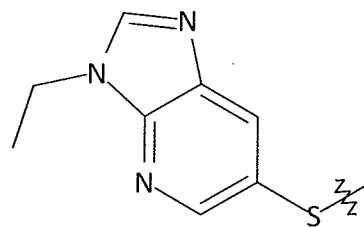
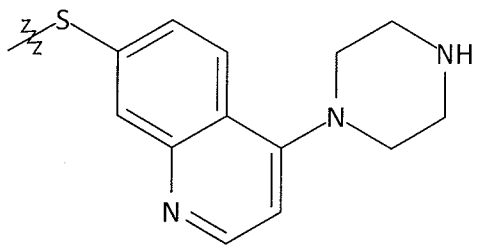
[0015] R² may be H, a hydrocarbyl residue (1-40C) containing 0-10 heteroatoms selected from O, S and N optionally substituted with an inorganic residue. R² may comprise at least one aryl or heteroaryl moiety. In some aspects, the aryl or a heteroaryl moiety of R² is directly linked to L. The at least one aryl or heteroaryl moiety of R² may be substituted with 0-4 alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroarylalkyl, NH-aroyl, arylacyl, heteroarylacyl, halo, O⁻ (if R² contains N), OR, NR₂, SR, SOR, SO₂R, OCOR, CONROR, NRCOR, NRCONR₂, NRCOOR, OCONR₂, COOR, SO₃R, CONR₂, CONR₂OR, SO₂NR₂, NRSO₂NR₂, CN, CF₃, or NO₂, wherein each R is independently H, alkyl, alkenyl or aryl or

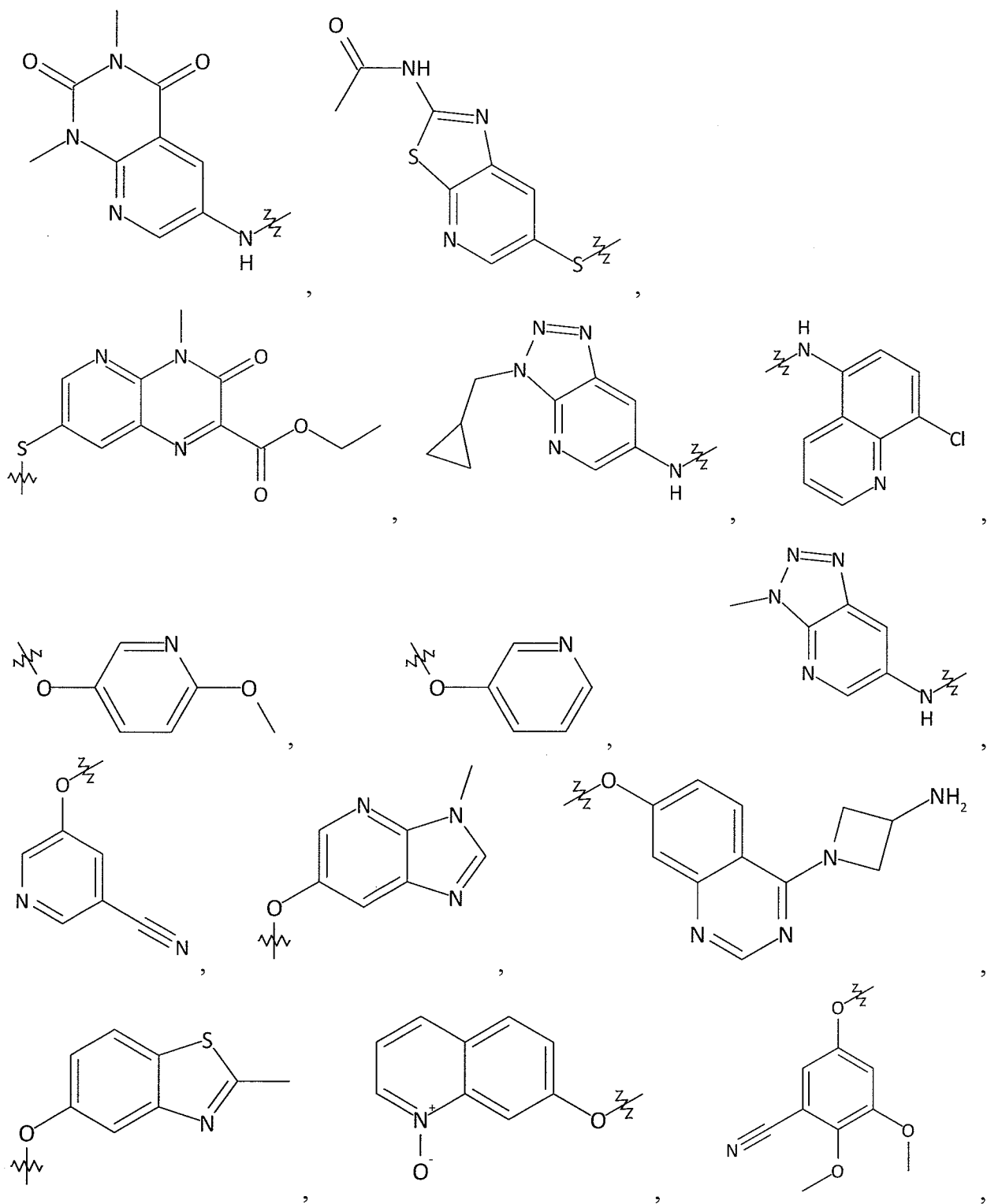
heteroforms thereof, and wherein two of said substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-14 members. Typically, the substituent may contain 1-15C, such as 1-10C, 1-6C or 1-3C, although it is understood that substituents such as alkenyl and alkynyl have at least two carbon atoms such as 2-15C, 2-10C, 2-6C, and 2-3C. In some aspects, the aryl or heteroaryl moiety of R^2 comprises at least one moiety selected from the group consisting of phenyl, pyrido[2,3-b]pyrazine, pyridyl, thiazole, quinoline, pyridazine, pyrimidinedione, pyrido[2,3-d]pyrimidinedione, pyrimidine, [1,2,3]triazolo[4,5-b]pyridine, oxazole, benzotriazine, furo[3,2-b]pyridine, thiazolo[5,4-b]pyridine, pyrazolo[3,4-b]pyridine, imidazo[4,5-b]pyridine, pyrido[3,2-d]pyrimidine, 1,5-naphthyridine, quinolone, quinazoline, and quinoxaline.

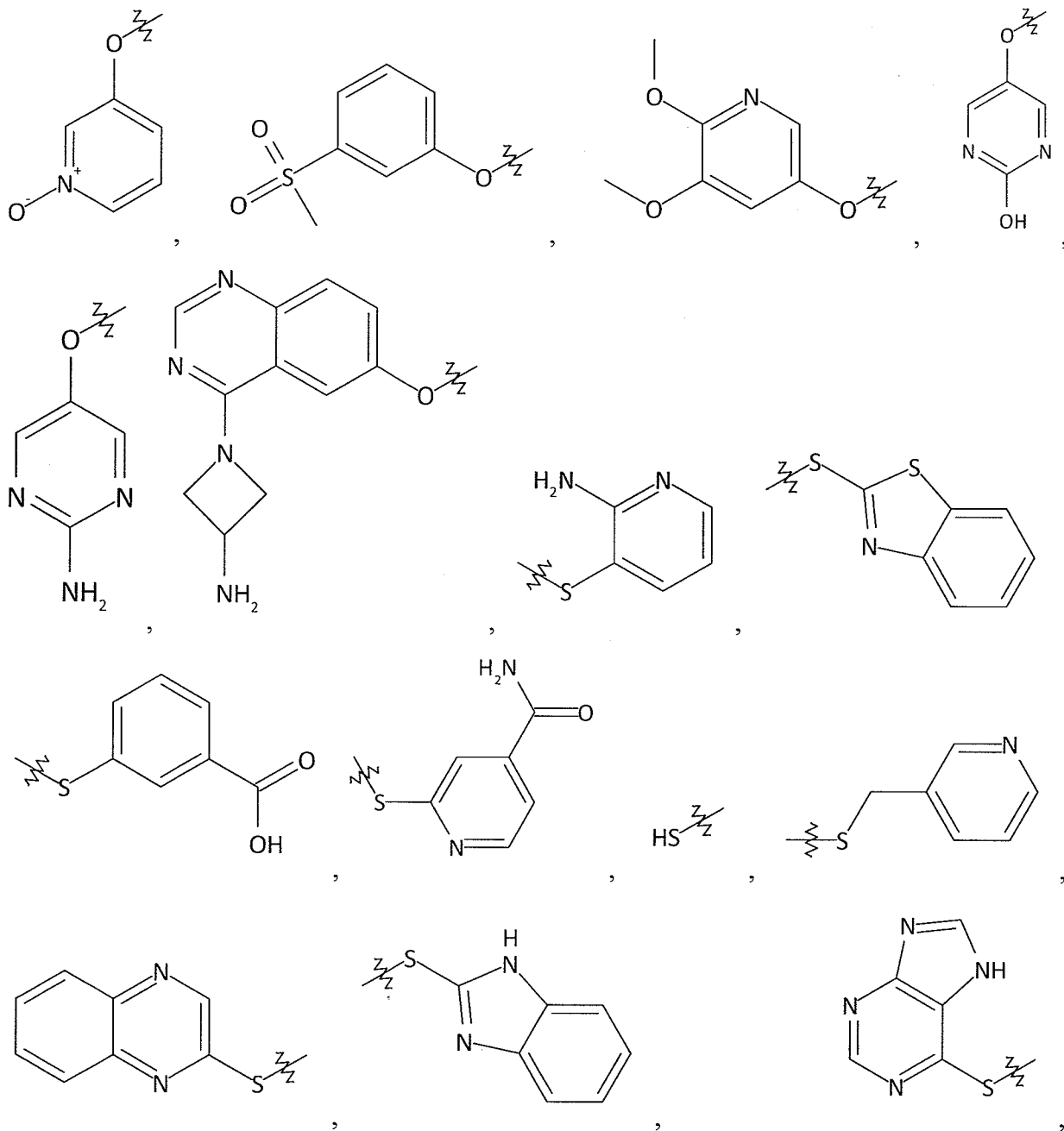
[0016] In some embodiments, $L-R^2$ may be one of

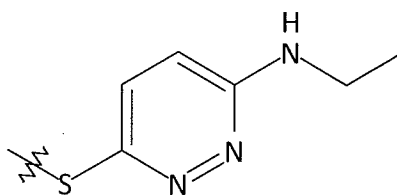
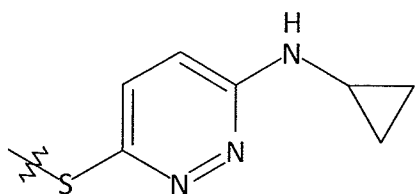
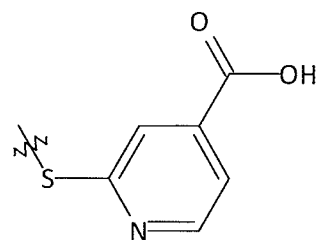
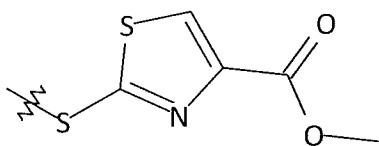
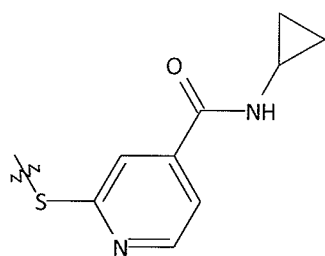
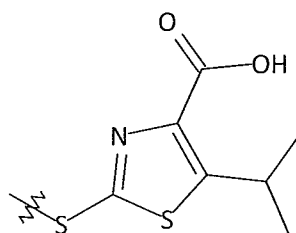
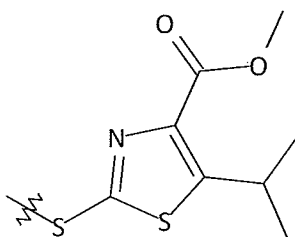
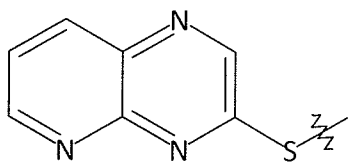
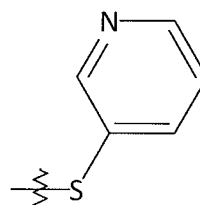
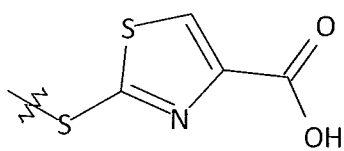
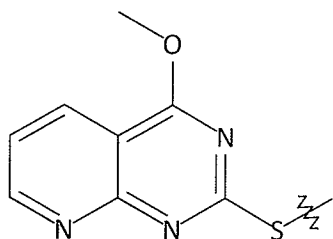
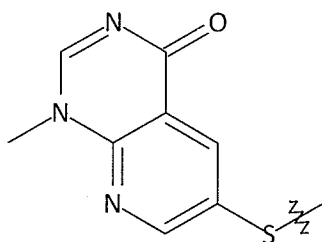
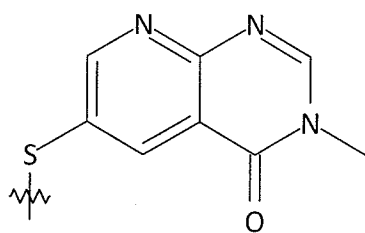
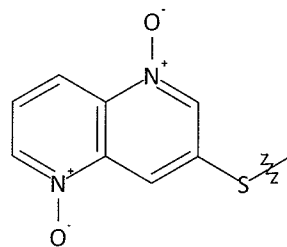
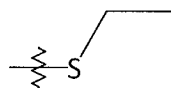
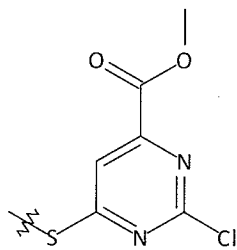
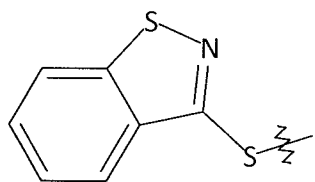


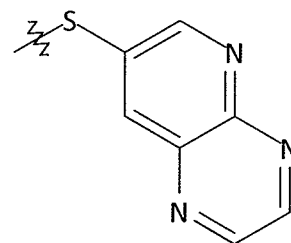
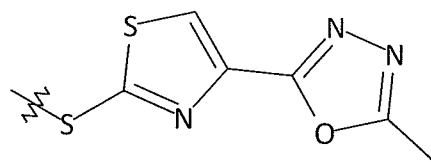
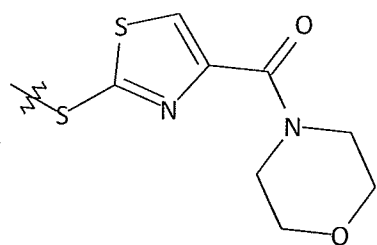
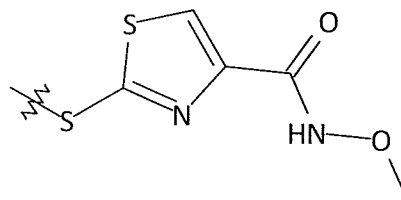
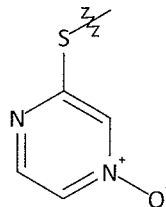
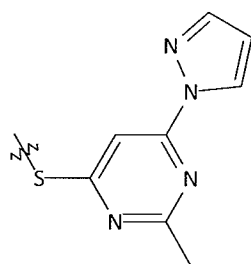
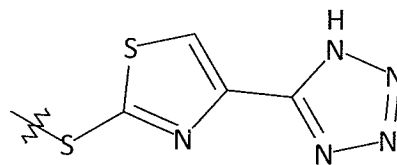
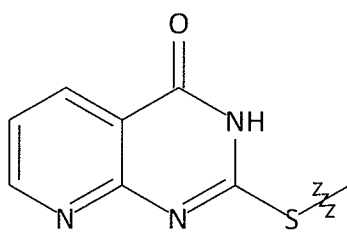
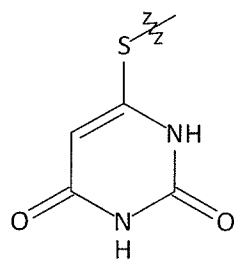
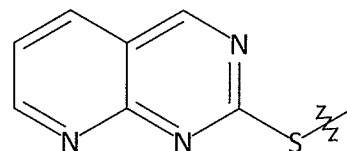
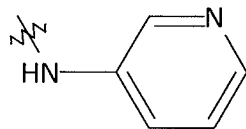
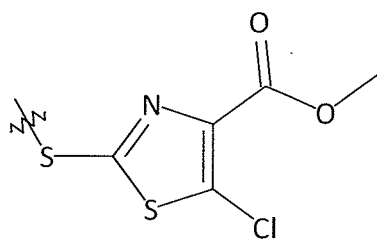
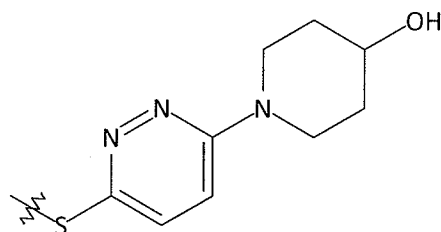
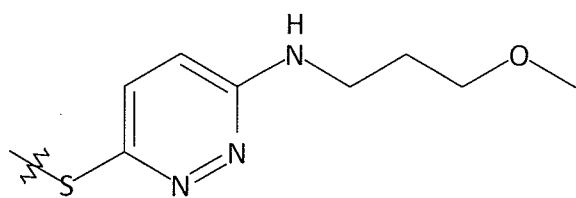


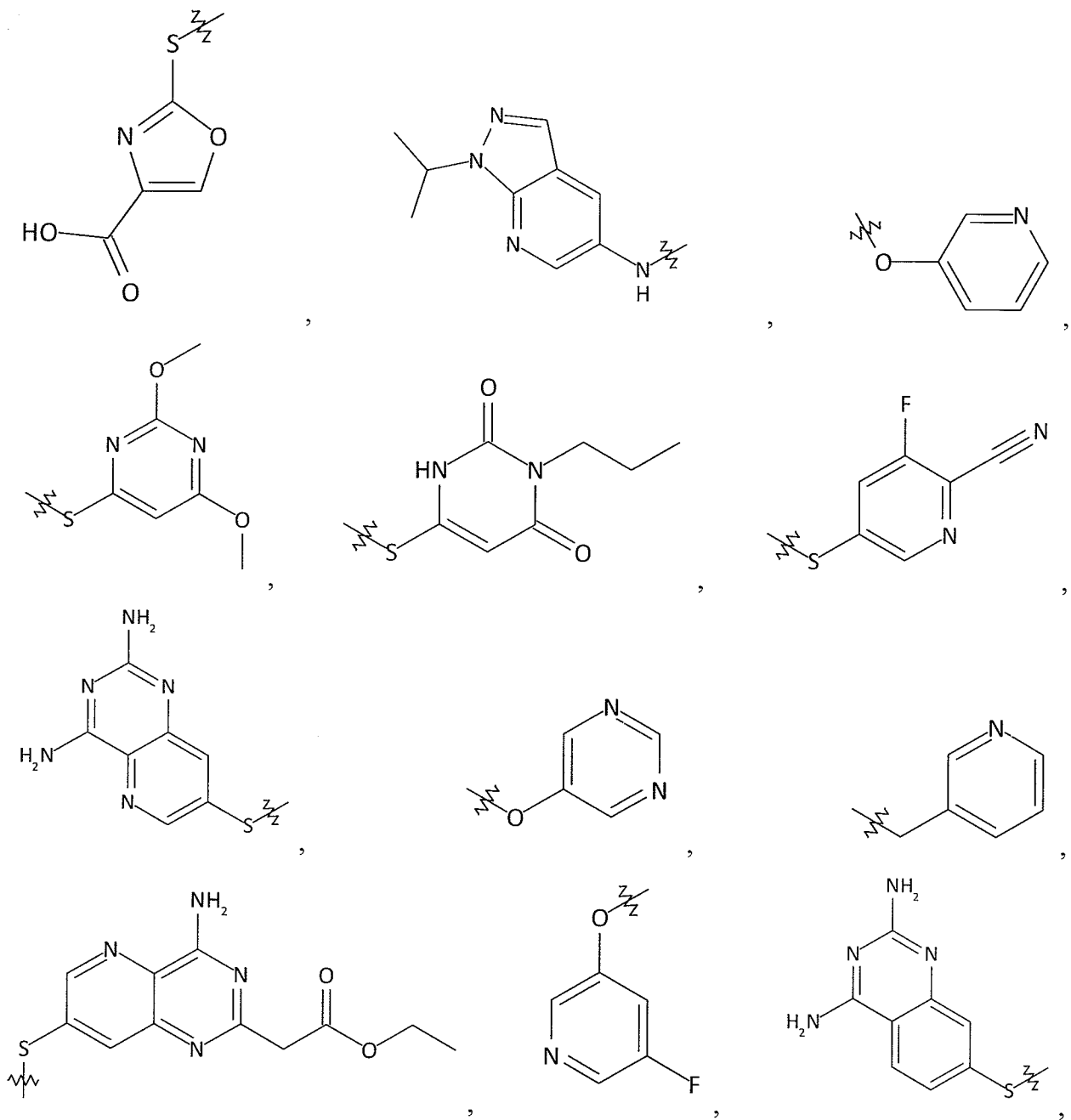


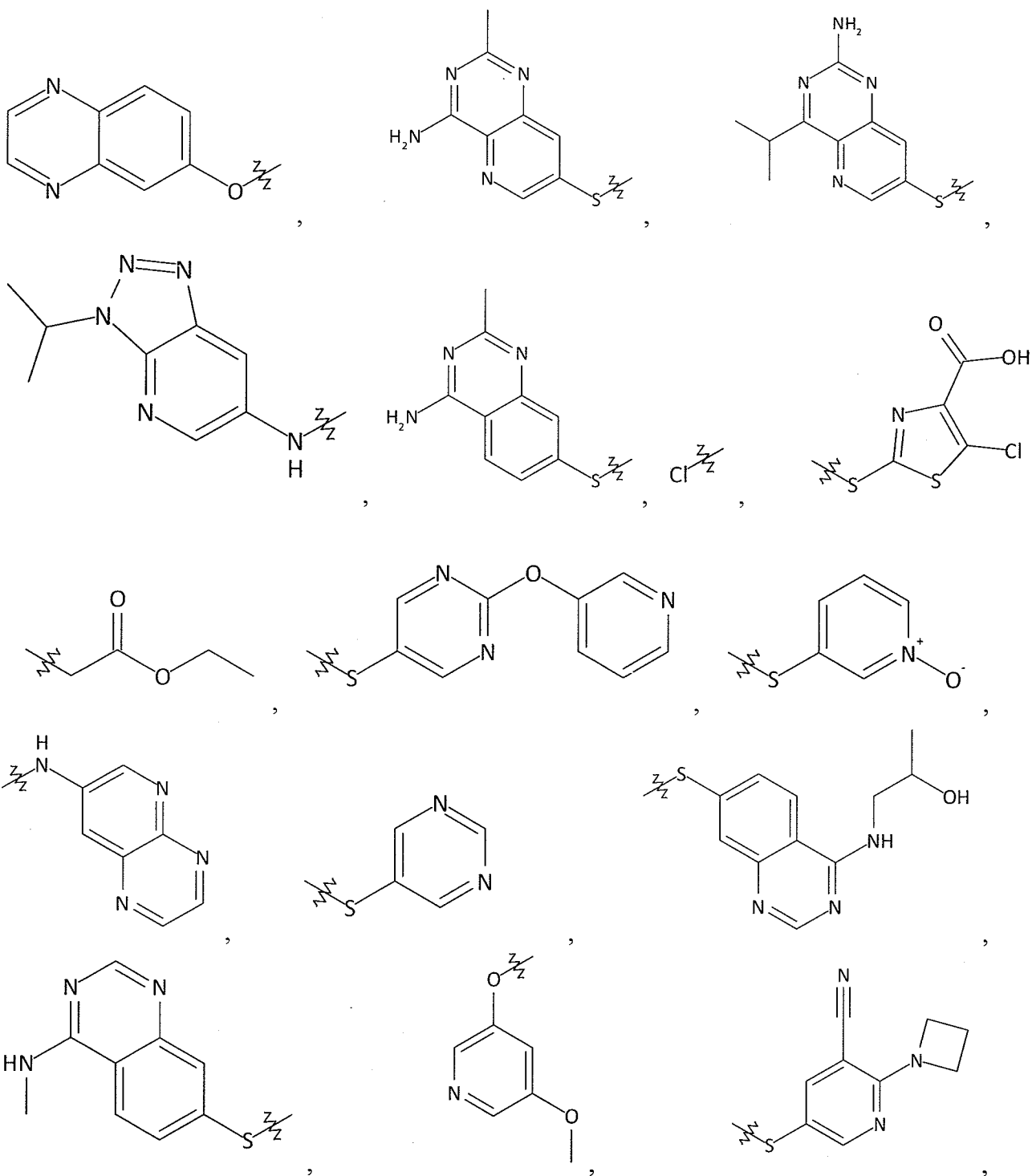


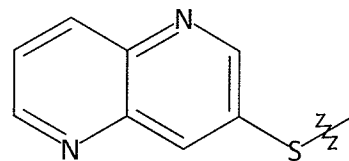
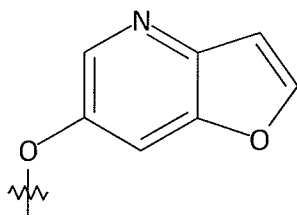
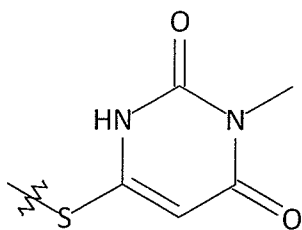
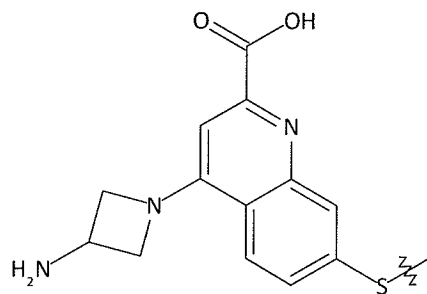
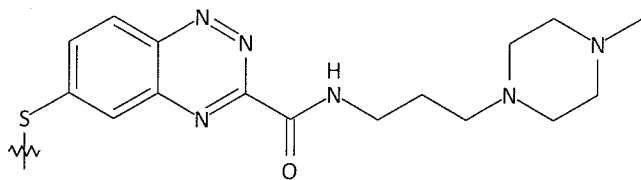
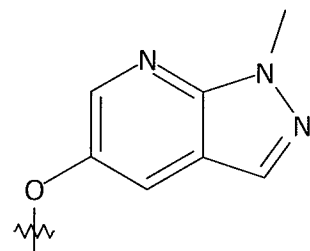
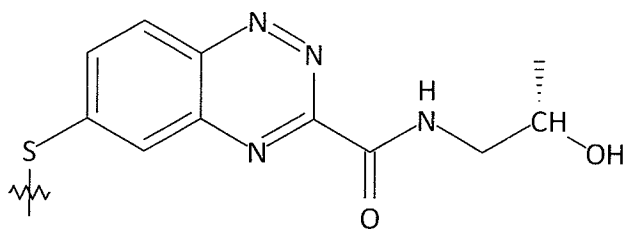
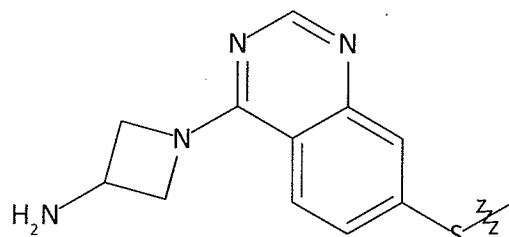
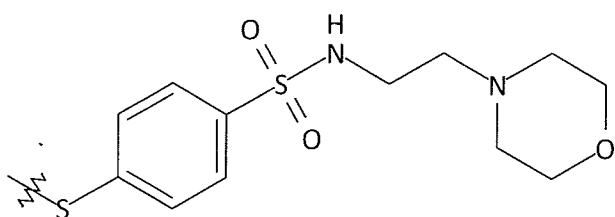
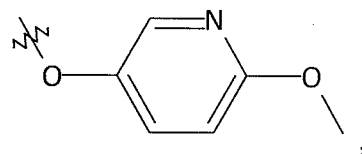
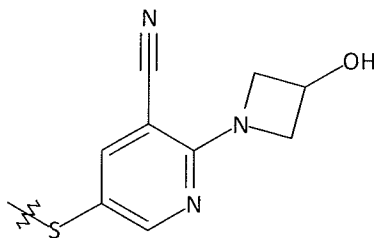


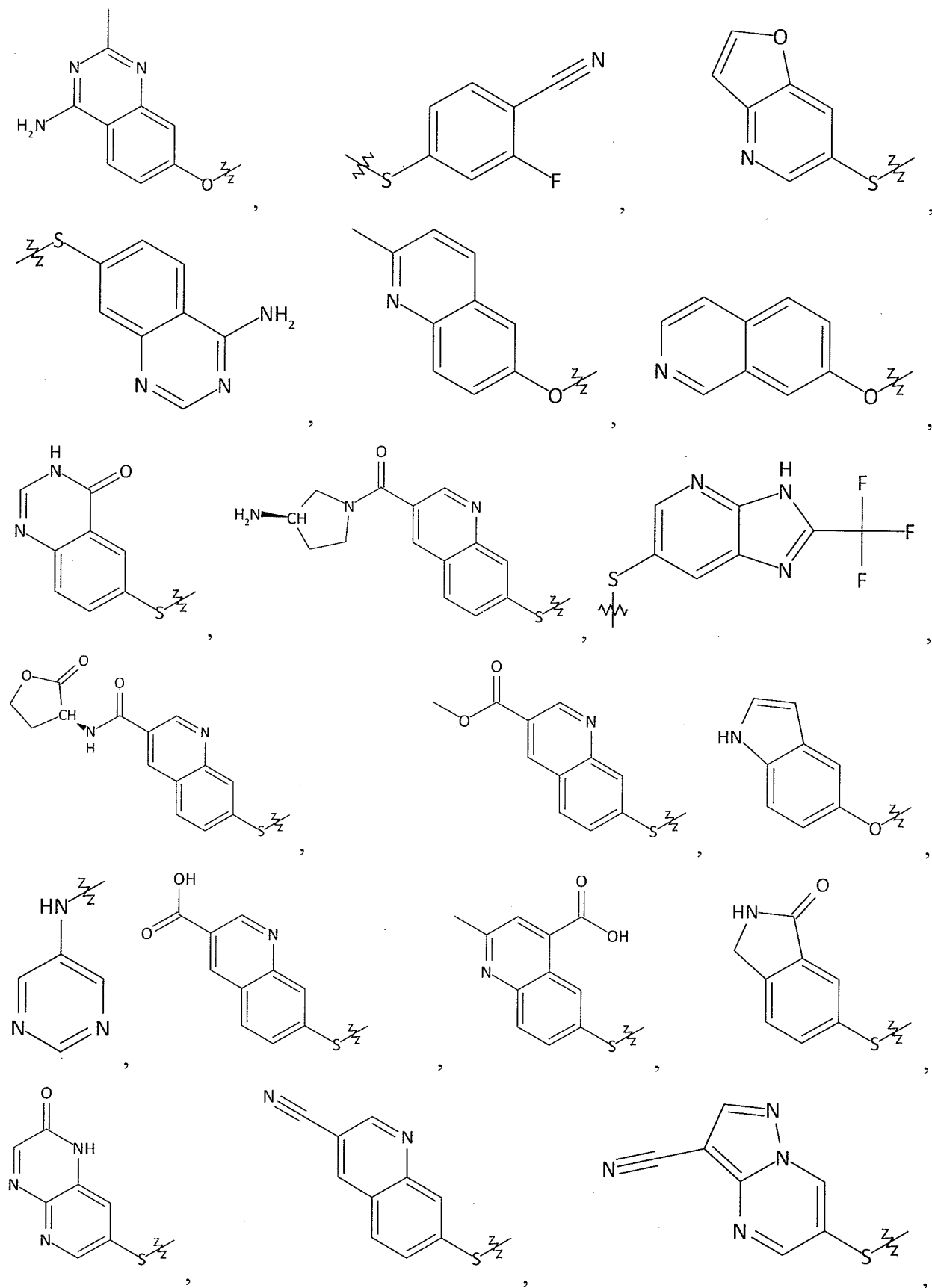


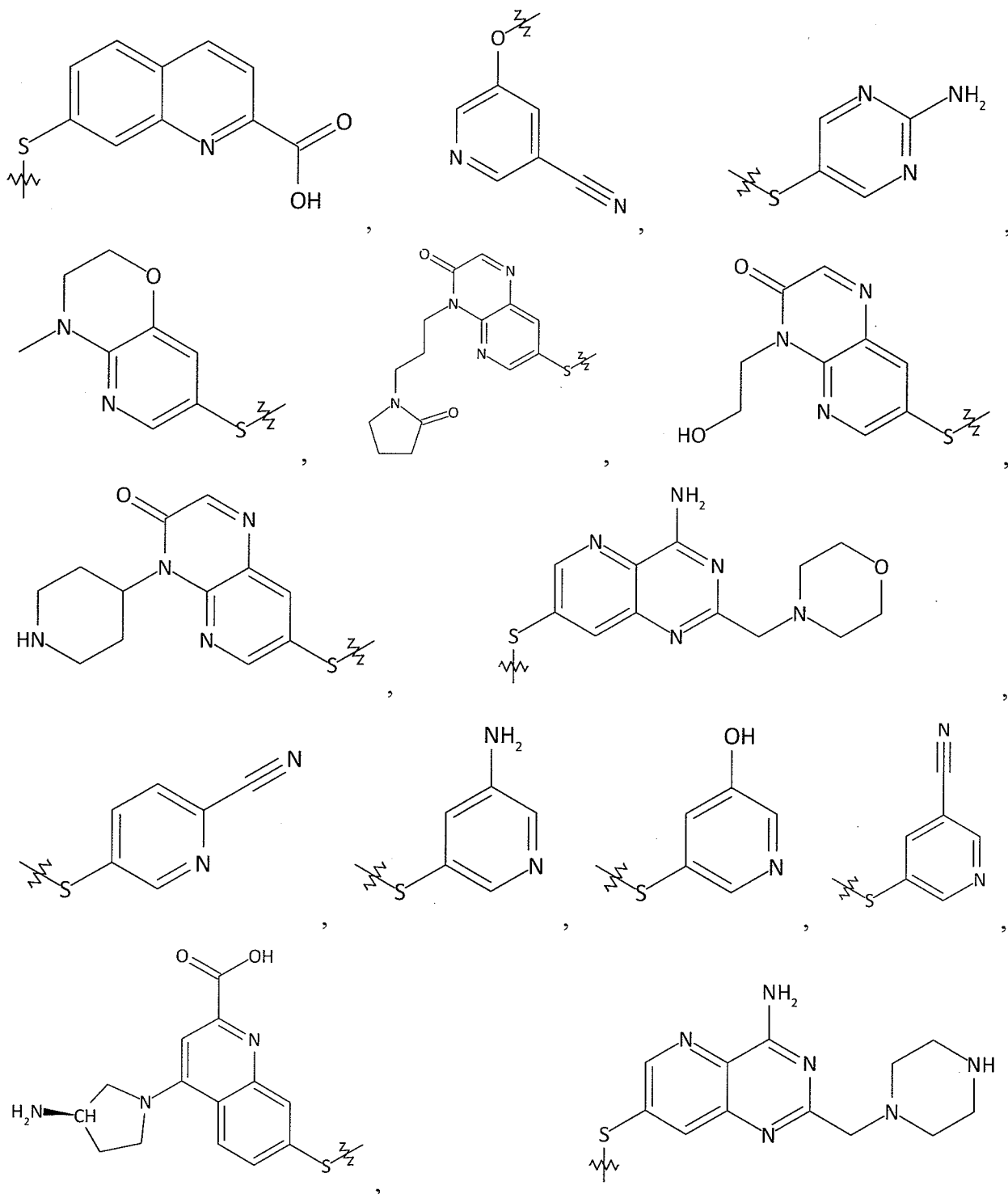


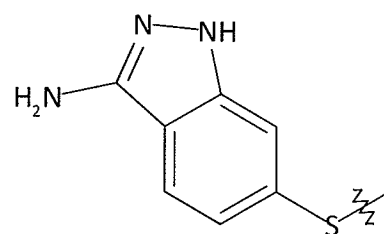
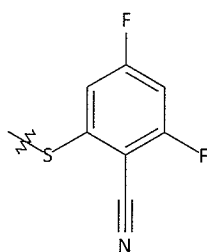
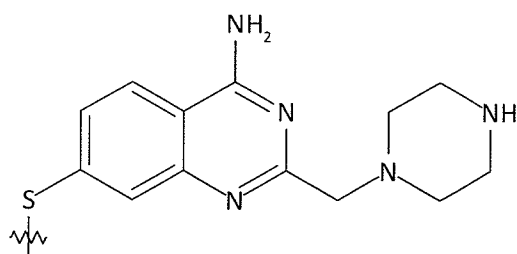
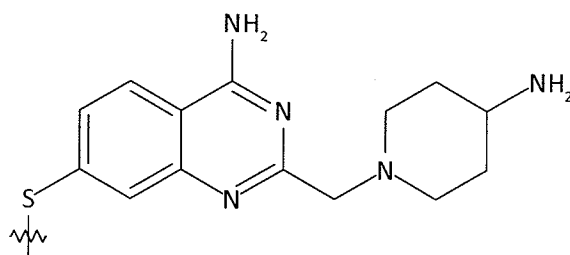
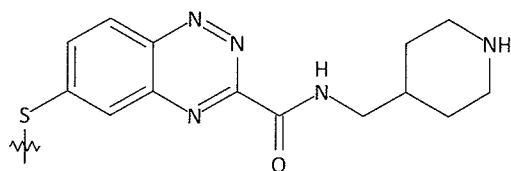
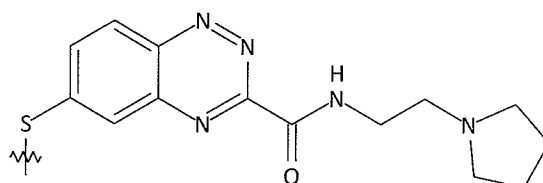
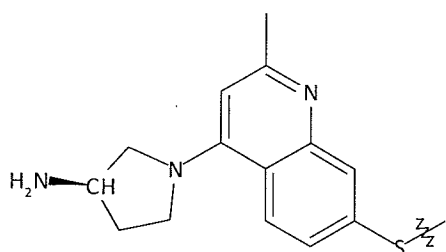
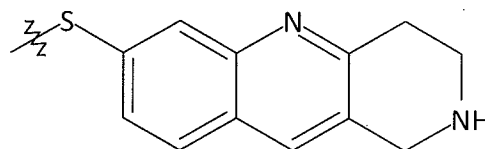
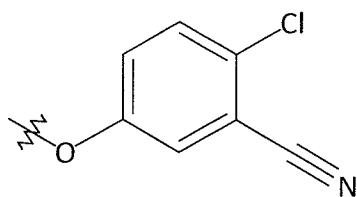
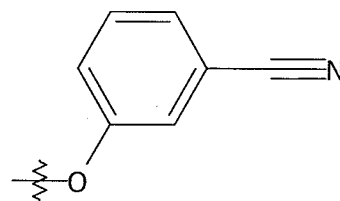
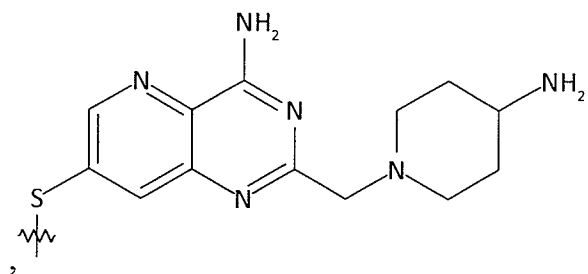


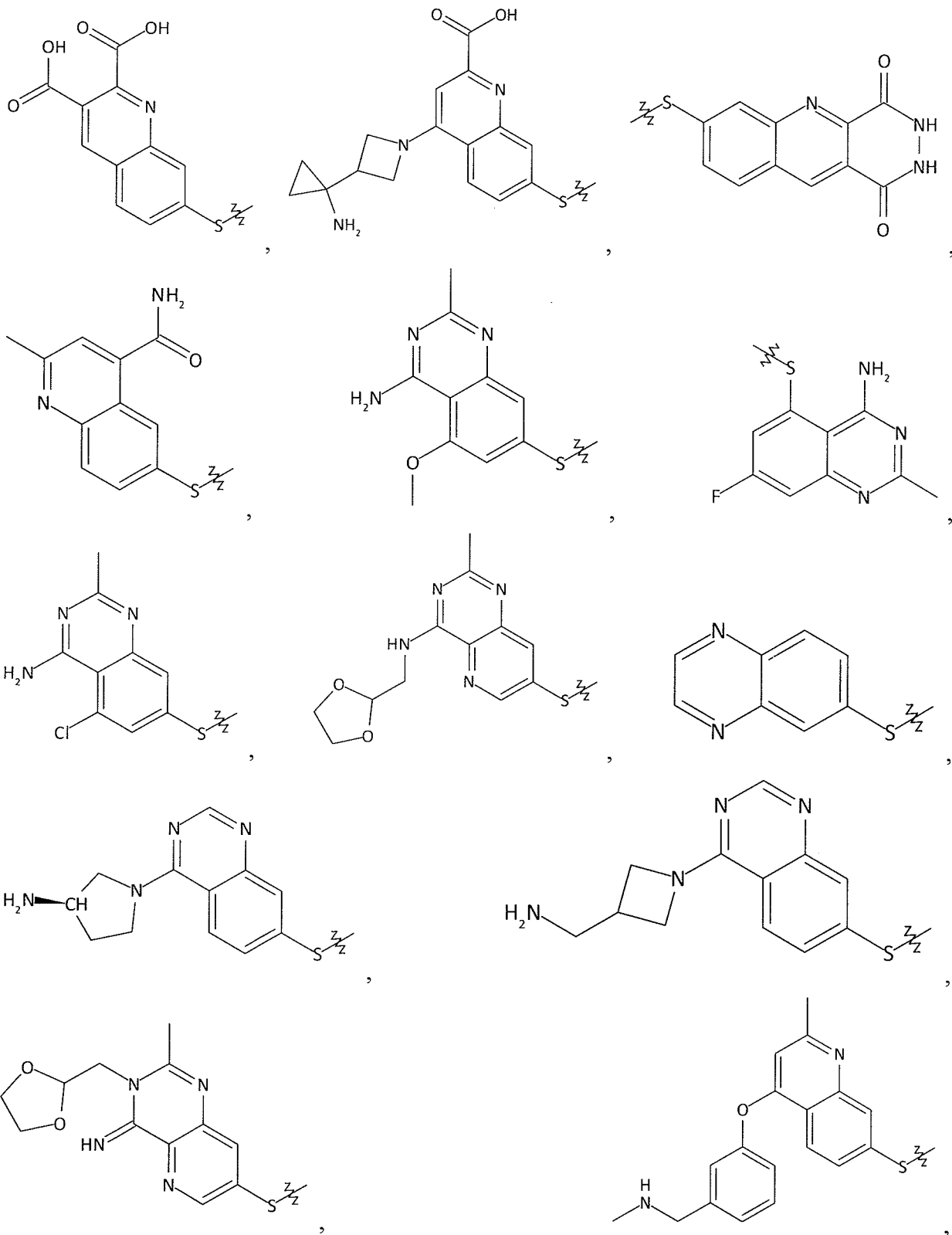


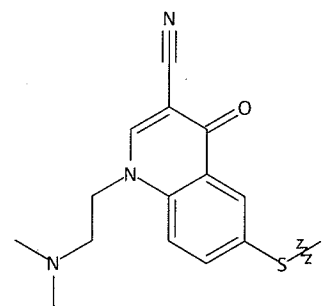
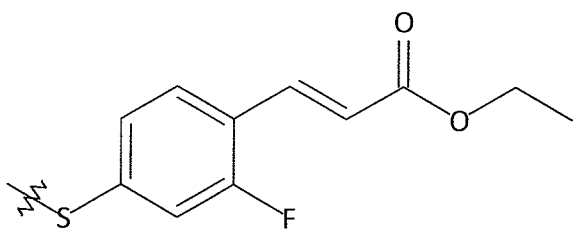
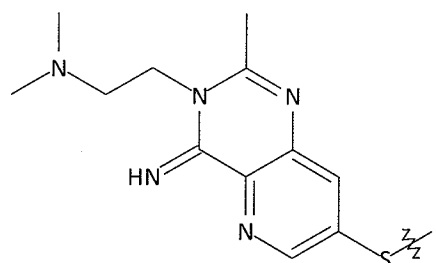
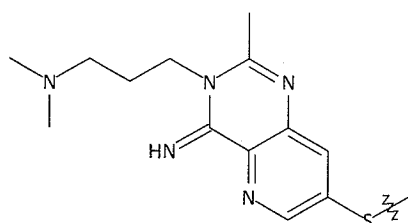
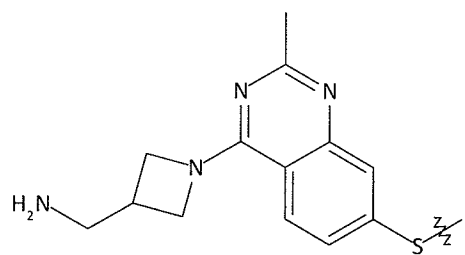
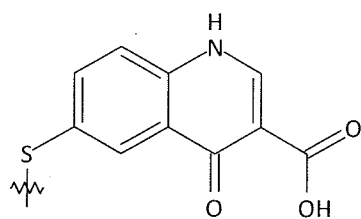
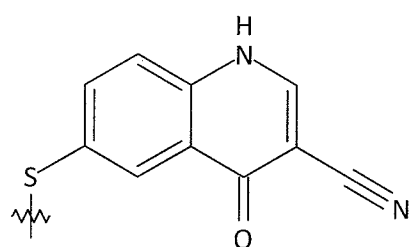
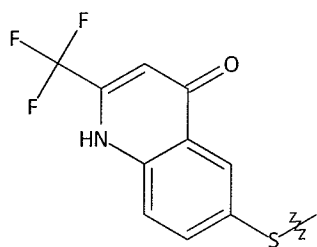
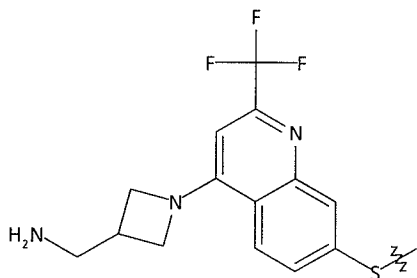
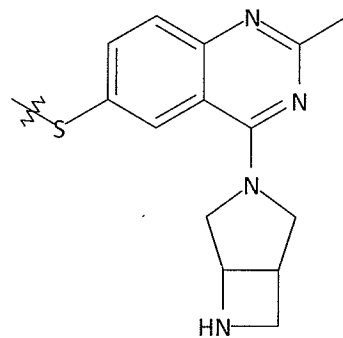
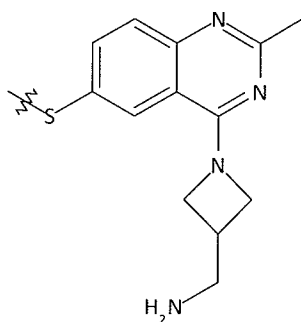
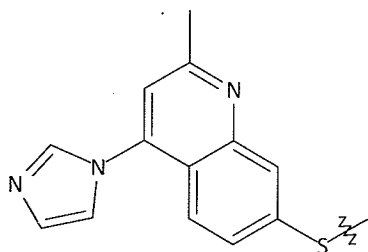


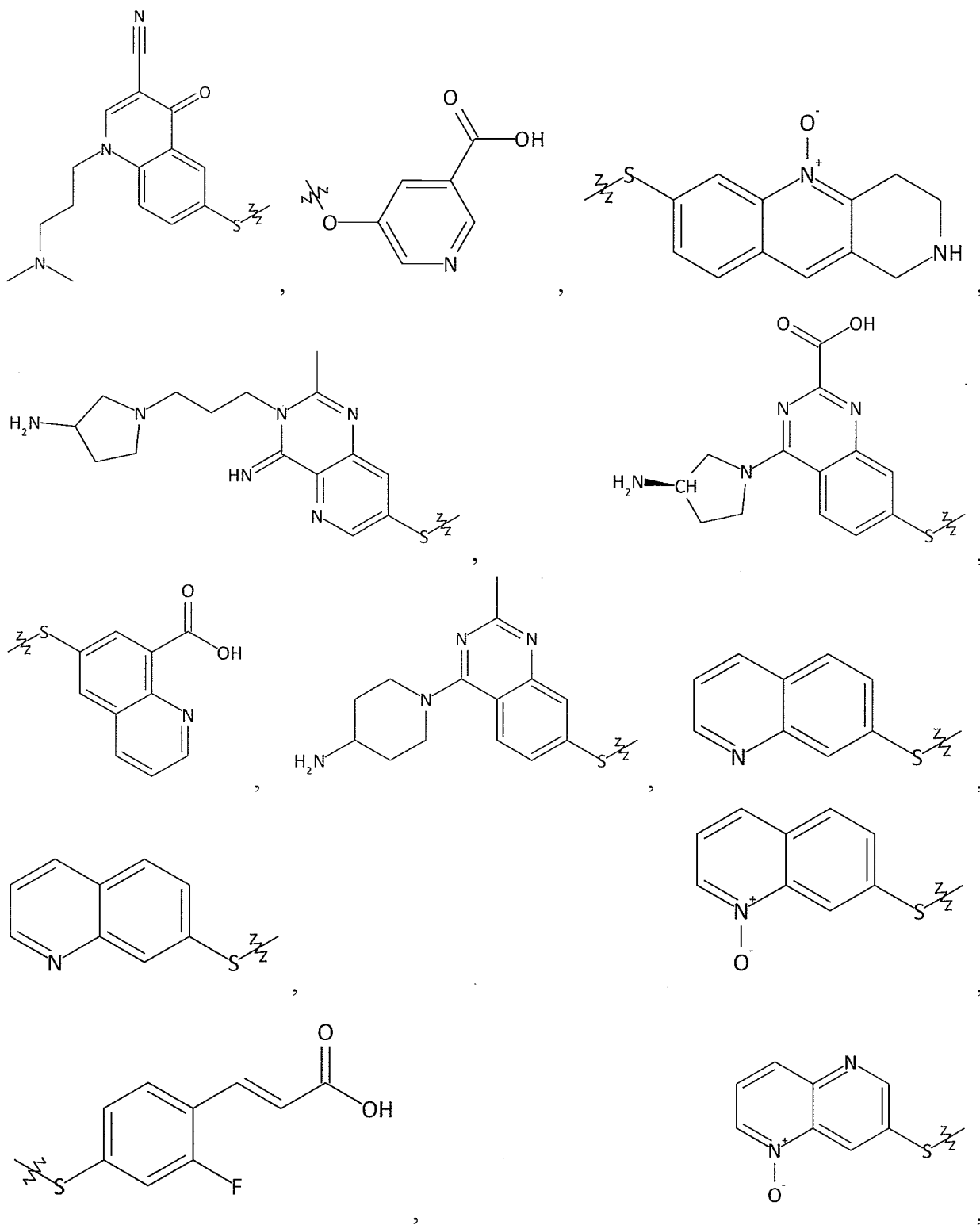


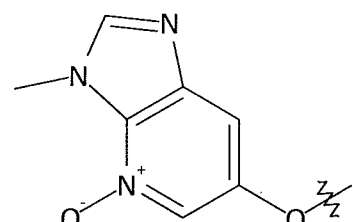
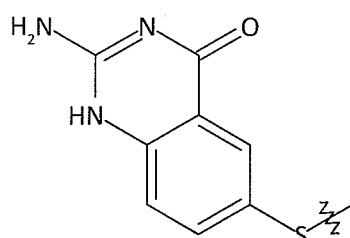
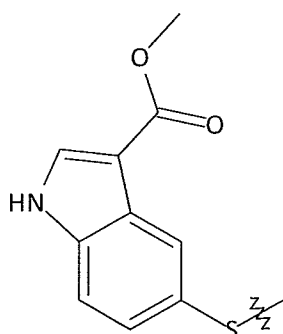
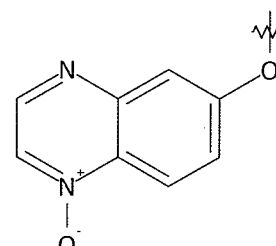
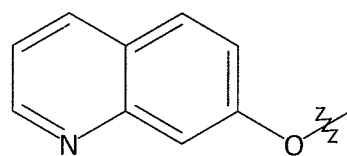
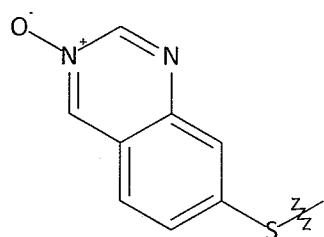
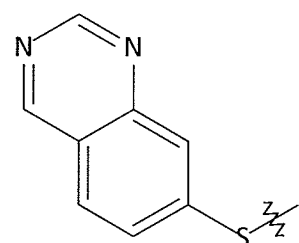
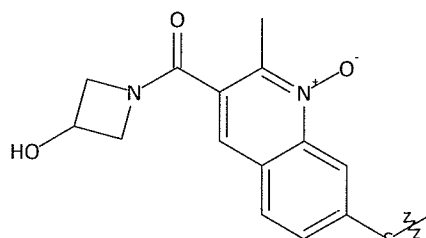
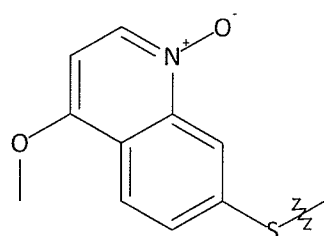
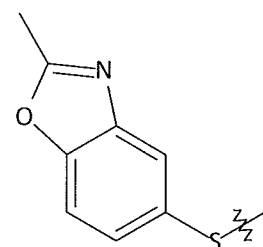
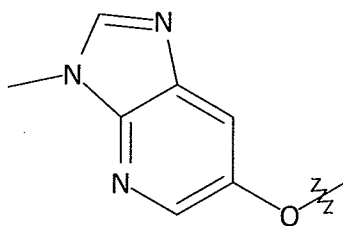
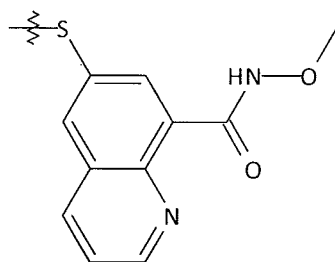
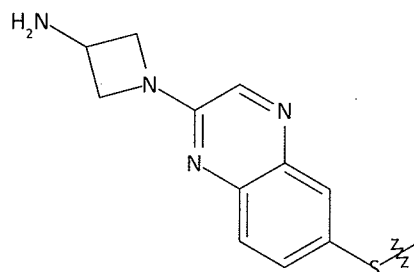
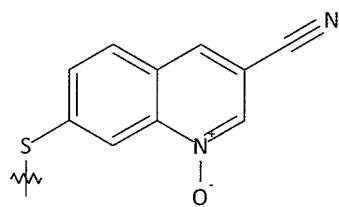
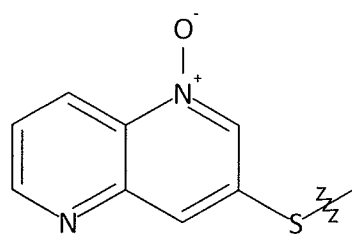


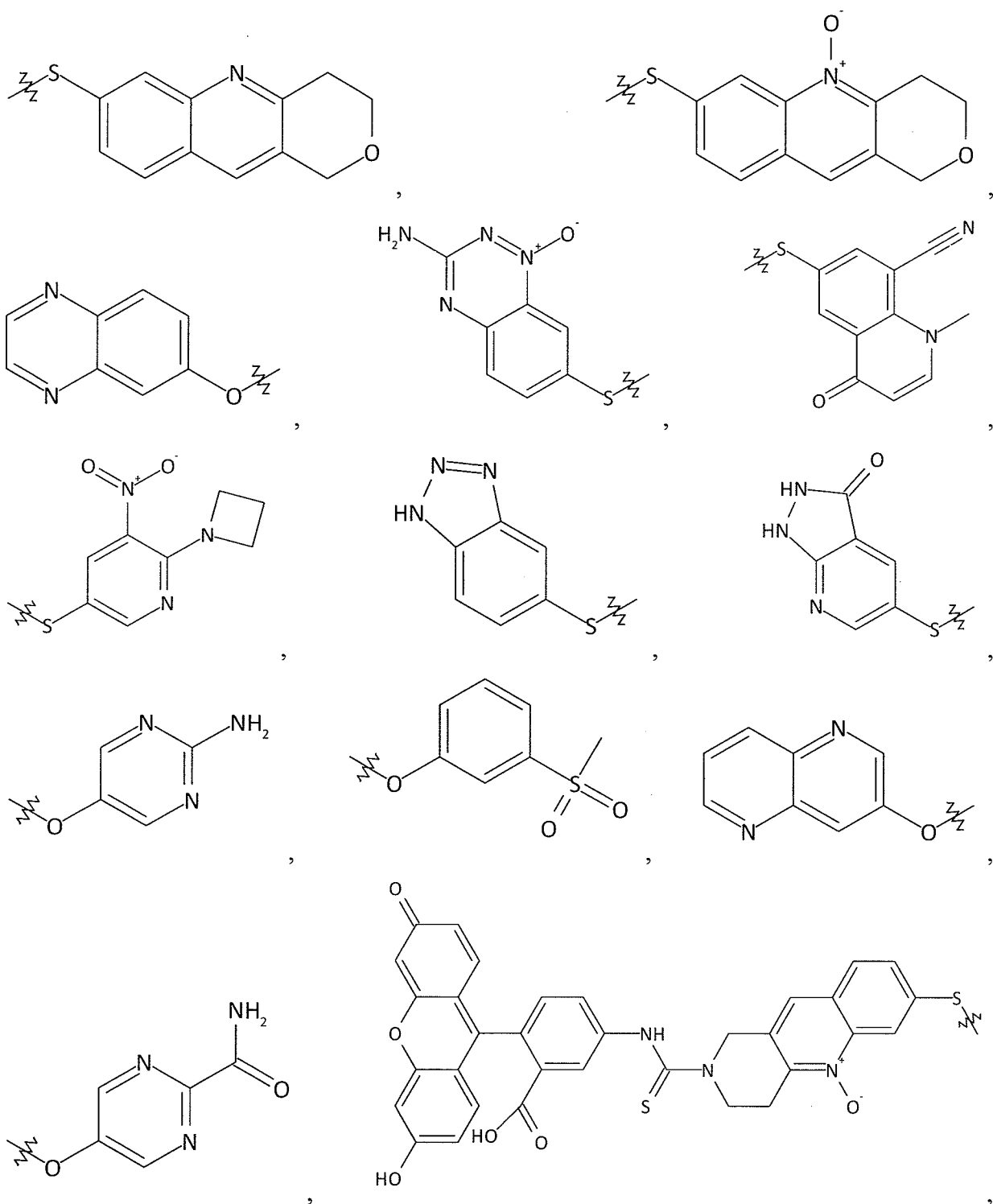


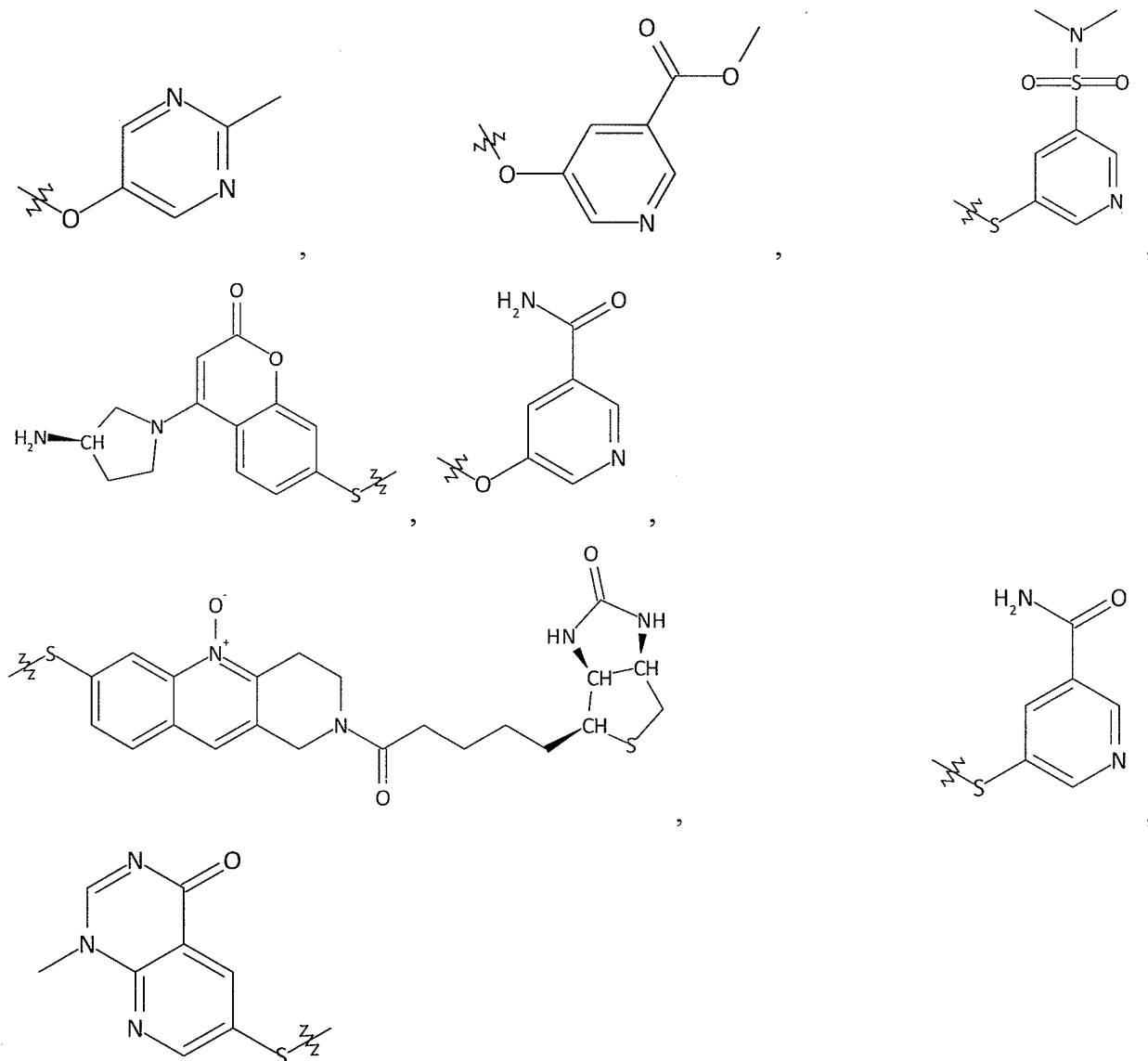












or

[0017] Of course, the linker L in the above embodiments may be interchanged with another linker described herein, such as O, S, NH, or CH₂.

[0018] R⁴ may be H, an inorganic residue, or a hydrocarbyl residue (1-30C) containing 0-12 heteroatoms selected from O, S and N and containing 0-10 inorganic residues, wherein R⁵ and R⁴ together may join to form a fused ring.

[0019] An inorganic residue of R⁴ may be H, halo, OH, NH₂, SH, SO₂H, NHOH, SO₃H, SO₂NH₂, or NHSO₂NH₂.

[0020] In some embodiments, a hydrocarbyl residue (1-30C) containing 0-12 heteroatoms selected from O, S and N of R⁴ may be an aryl C₅₋₁₄ or heteroaryl C₁₋₁₄ moiety that

may be substituted with 0-10 substituents selected from alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroarylalkyl, NH-aroyl, arylacyl, heteroarylacyl, halo, -O (if R⁴ contains N), OR', NR'₂, SR', SOR', SO₂R', OCOR', N-alkyl-OR', CONR'OR', NR'COR', NR'CONR'₂, NR'COOR', OCONR'₂, OR', NR'₂, COOR', alkyl-OOR', SO₃R', CONR'₂, CONR'₂OH, SO₂NR'₂, NR'SO₂NR'₂, CN, CF₃, or NO₂, wherein each R' is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-14 members.

[0021] In some embodiments, a hydrocarbyl residue (1-30C) containing 0-12 heteroatoms selected from O, S and N of R⁴ may be an alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, or heteroarylalkynyl moiety substituted with 0-10 substituents selected from the group consisting of: aryl, haloaryl, arylalkyl, arylalkenyl, arylalkynyl, haloaryl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, acyl, aroyl, NH-aroyl, arylacyl, heteroarylacyl, halo, -O (if R⁴ contains N), =O, =NH, OR'', NR''₂, SR'', SOR'', SO₂R'', OCOR'', CONR''OR'', NR''COR'', NR''CONR''₂, NR''COOR'', NR''COCOOR'', OCONR''₂, COOR'', SO₃R'', CONR''₂, CONR''₂OH, SO₂NR''₂, NR''SO₂R'', NR''SO₂NR''₂, CN, CF₃, or NO₂, wherein each R'' is independently H, optionally substituted alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl, or halo forms thereof, and wherein two of said substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-14 members.

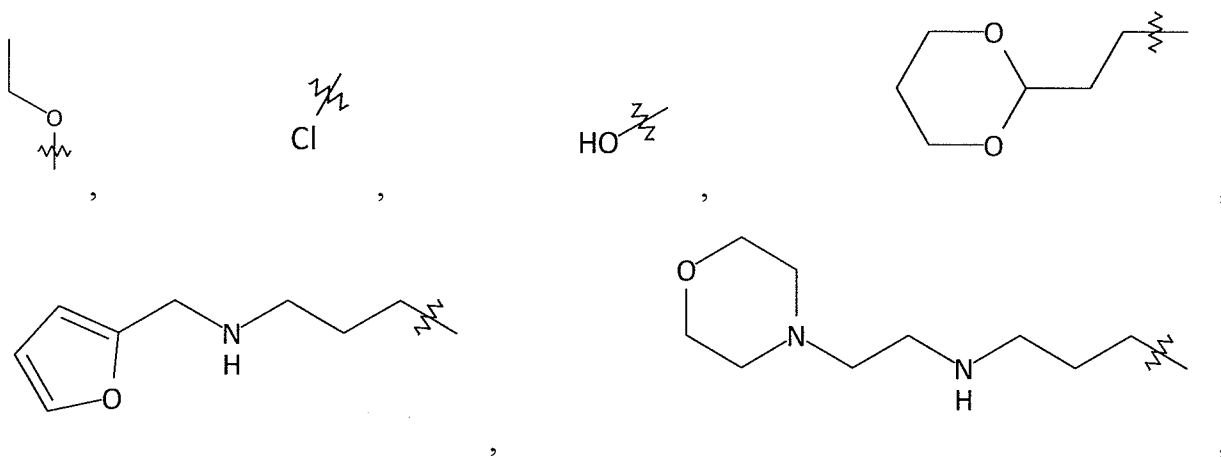
[0022] In further embodiments, a hydrocarbyl residue (1-30C) containing 0-12 heteroatoms selected from O, S and N of R⁴ may be OR''', NR'''₂, or OSO₂R''', wherein R''' is an aryl C₅₋₁₄ or heteroaryl C₁₋₁₄ moiety substituted with 0-10 substituents selected from alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroarylalkyl, NH-aroyl, arylacyl, heteroarylacyl, halo, -O (if R⁴ contains N), OR', NR'₂, SR', SOR', SO₂R', OCOR', N-alkyl-OR', CONR'OR', NR'COR', NR'CONR'₂, NR'COOR', OCONR'₂, COOR', alkyl-OOR', SO₃R', CONR'₂, CONR'₂OH, SO₂NR'₂, NR'SO₂NR'₂, CN, CF₃, or NO₂, wherein each R' is independently H,

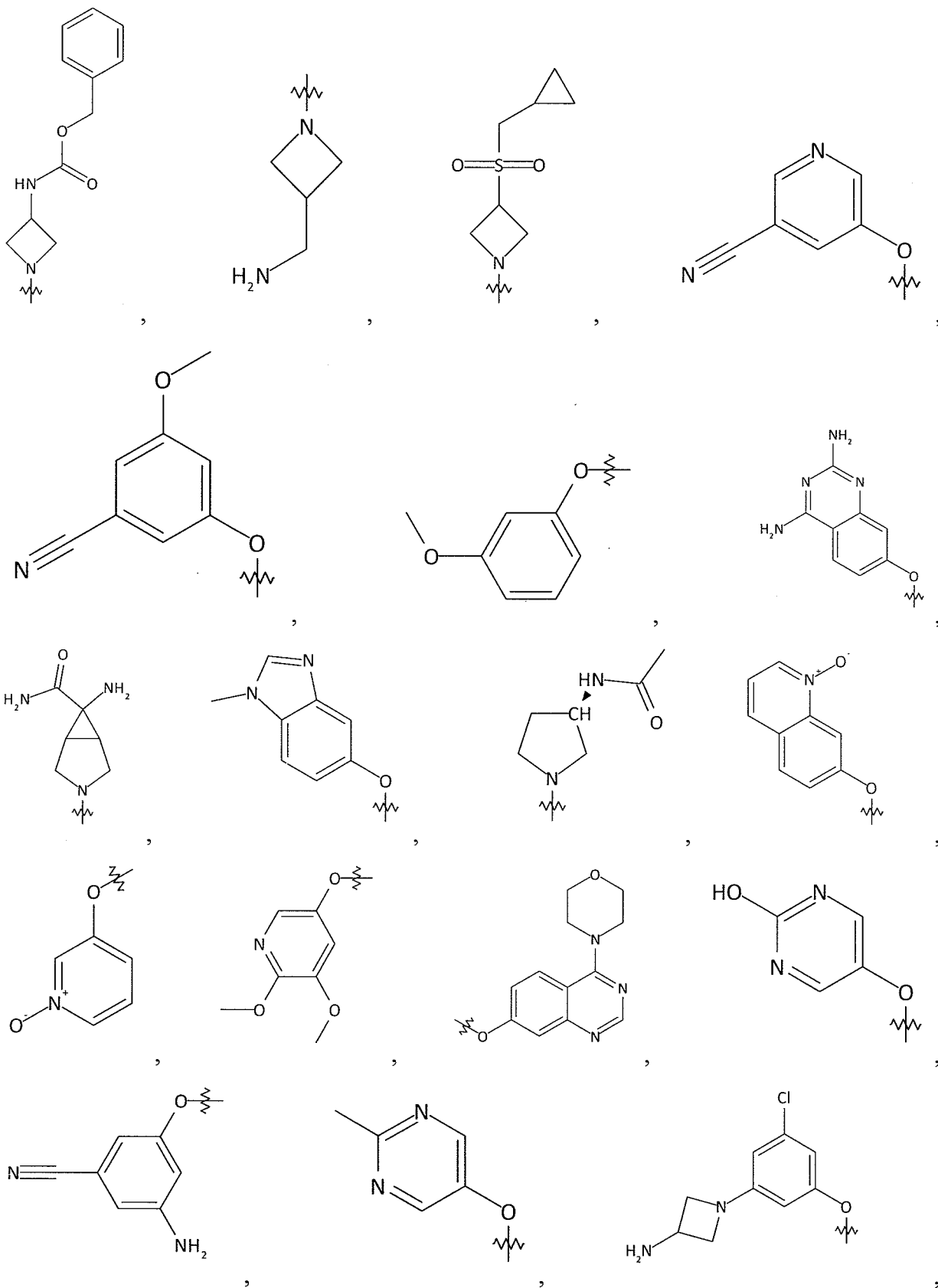
alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-14 members.

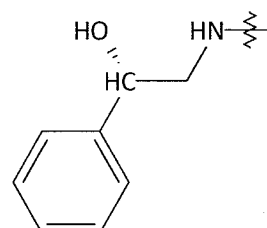
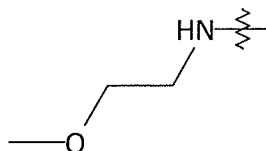
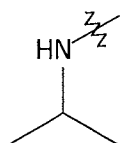
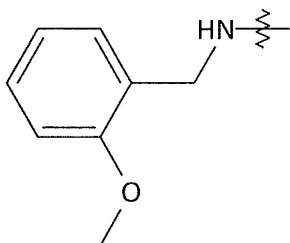
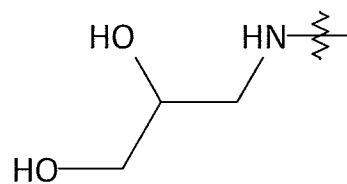
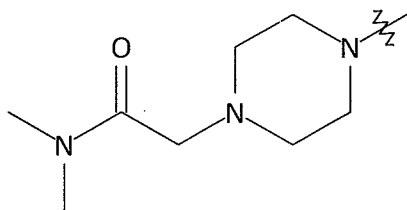
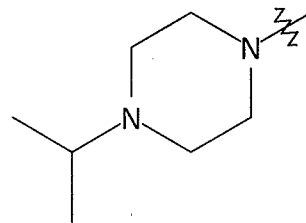
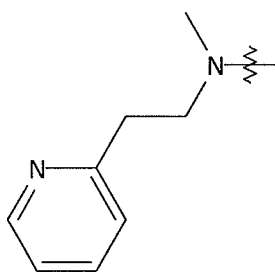
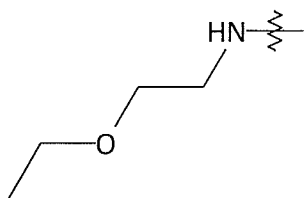
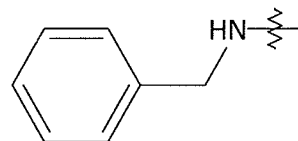
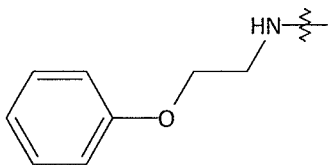
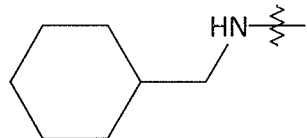
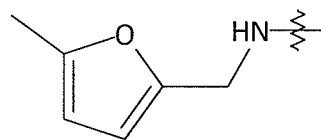
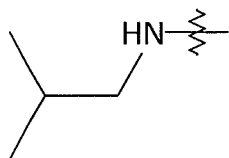
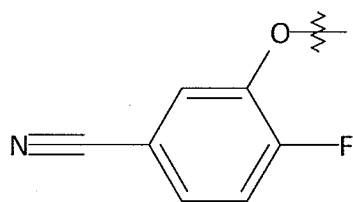
[0023] In some aspects, R^4 may be selected from the group consisting of

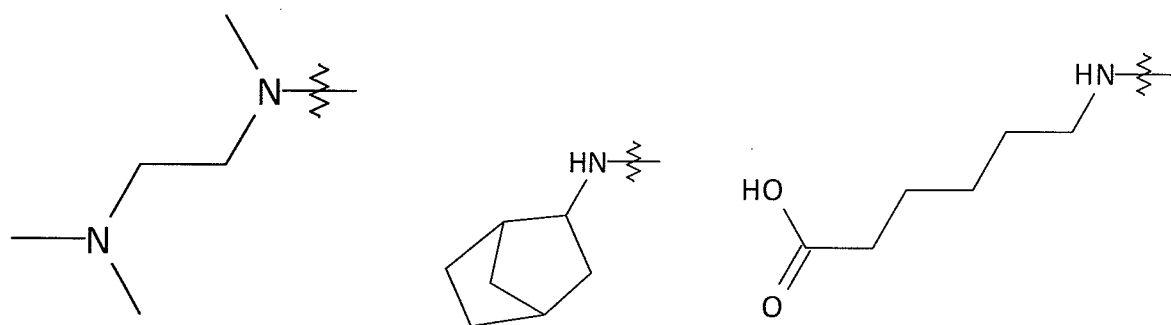
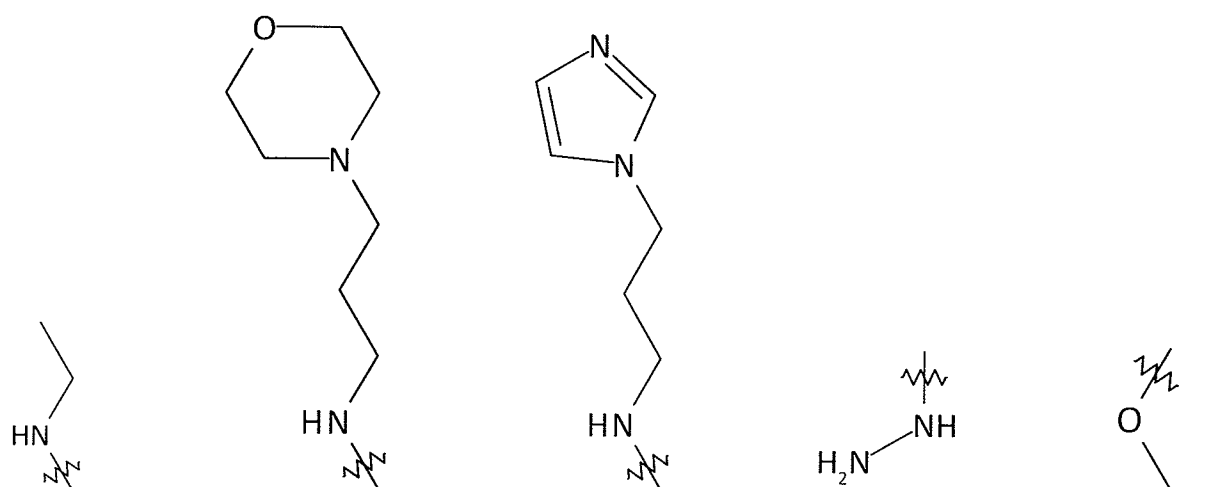
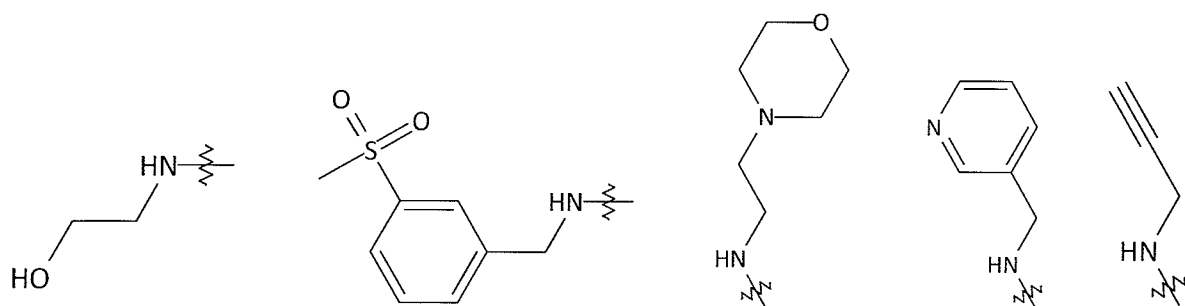
- a) H, halo, or OH;
- b) C3-6 heteroaryl moiety containing 1-4 heteroatoms selected from O, S, and N;
- c) an alkyl, alkenyl, arylalkenyl, arylalkyl, heteroalkyl, heteroalkynyl, heteroarylalkyl, moiety substituted with 0-10 substituents selected from the group consisting of: haloaryl, haloheteroaryl, heteroaryl, acyl, aroyl, NH-aroyl, halo, =O, =NH, OR'', NR''₂, SO₂R'', NR''CONR''₂, NR''COOR'', NR''COCOOR'', COOR'', NR''SO₂R'', wherein each R'' is independently H, optionally substituted alkyl, aryl, heteroalkyl, heteroaryl, optionally substituted with one or more halo, OH, CN, or =O and wherein two of said substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-14 members; or
- d) OR''', NR'''₂, or OSO₂R''', wherein R''' is aryl C₅₋₁₄ or heteroaryl C₁₋₁₄ containing 1-5 O, S, or N substituted with 0-3 substituents selected from alkyl, acyl, aroyl, heteroalkyl, halo, -O (if R⁴ contains N), OR', NR'₂, NHCOR', NHCO₂R', NHCONHR', SO₂R', COOR', CN, wherein each R' is independently H, alkyl.

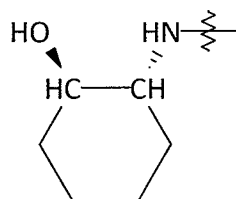
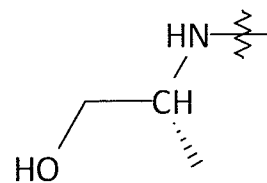
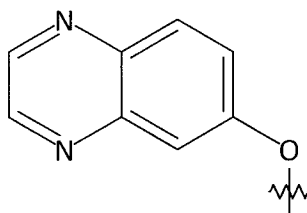
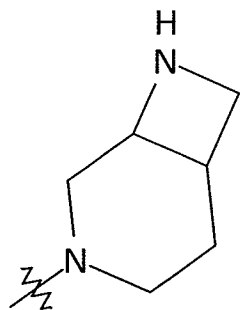
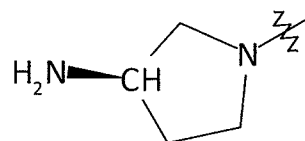
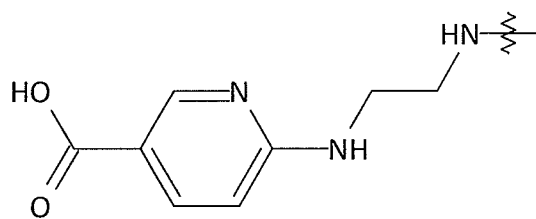
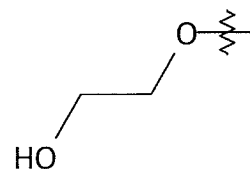
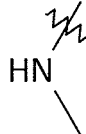
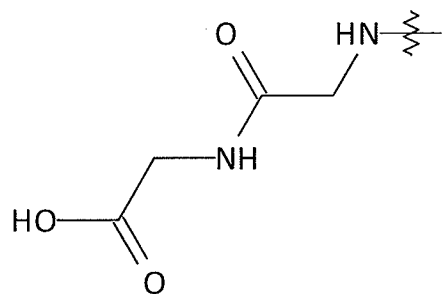
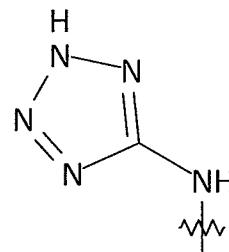
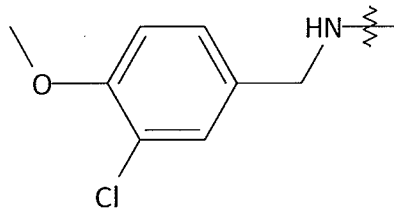
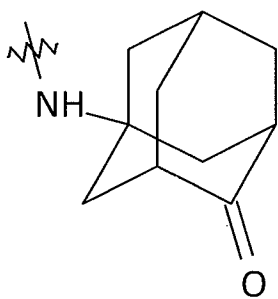
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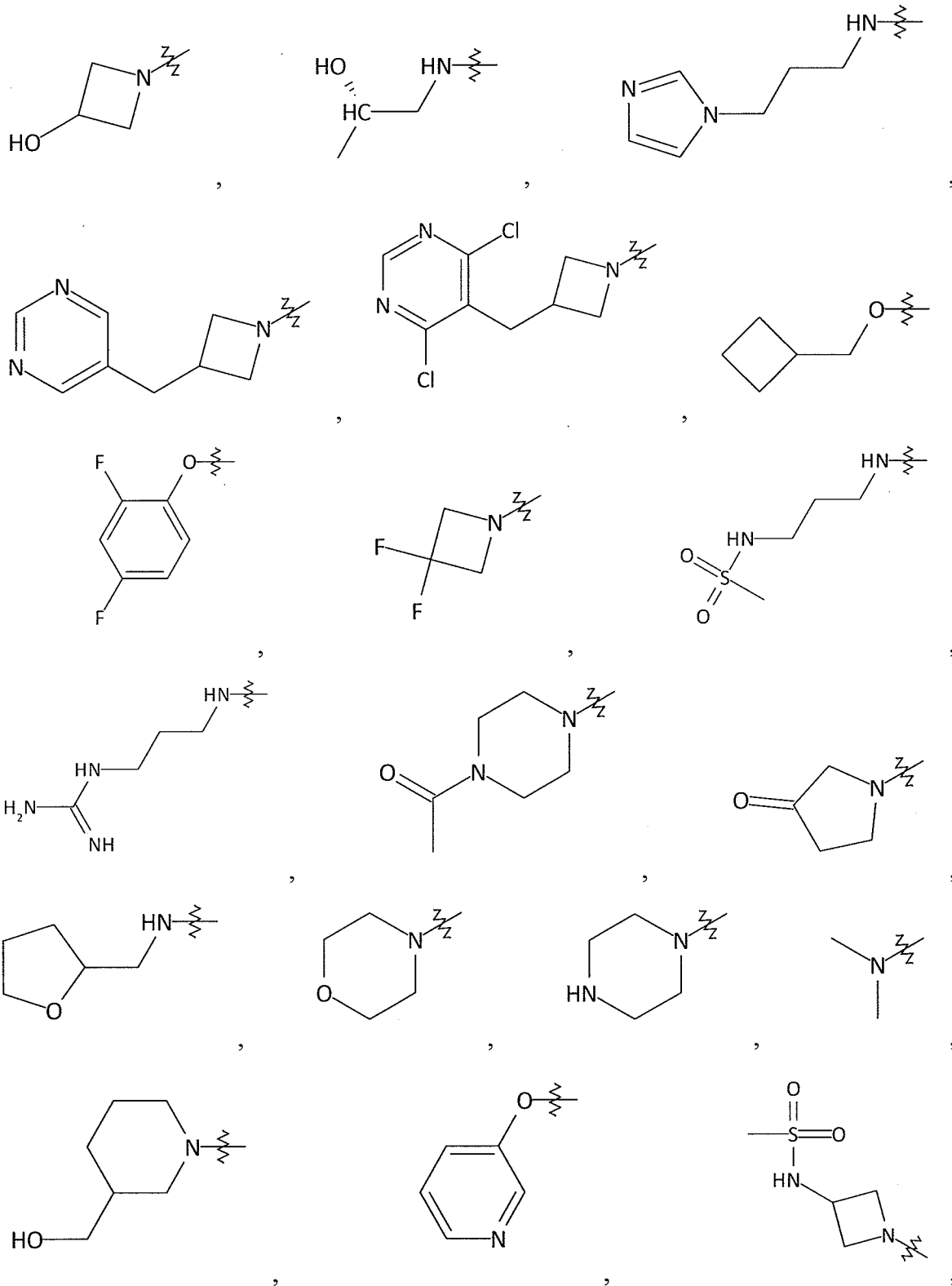


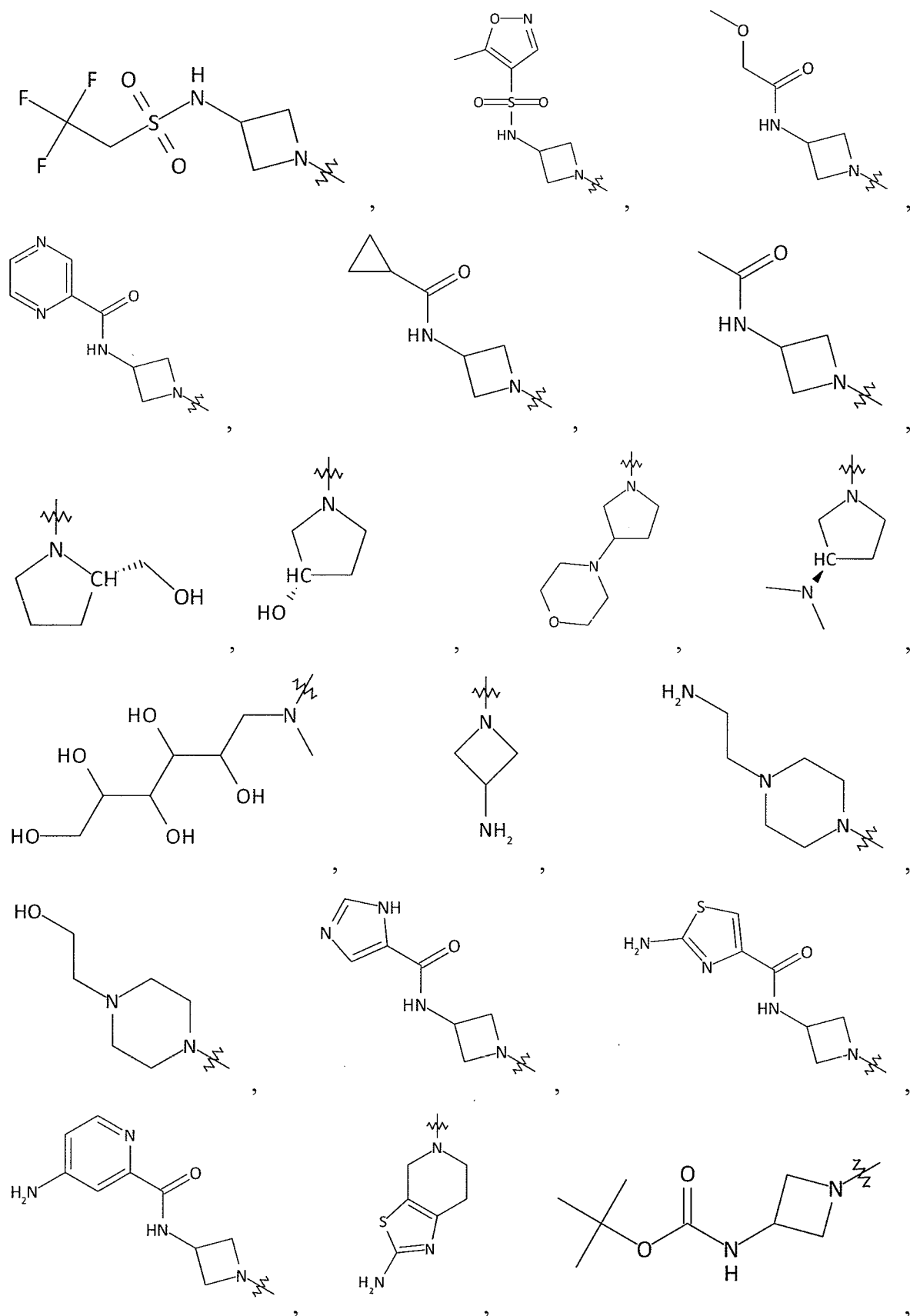


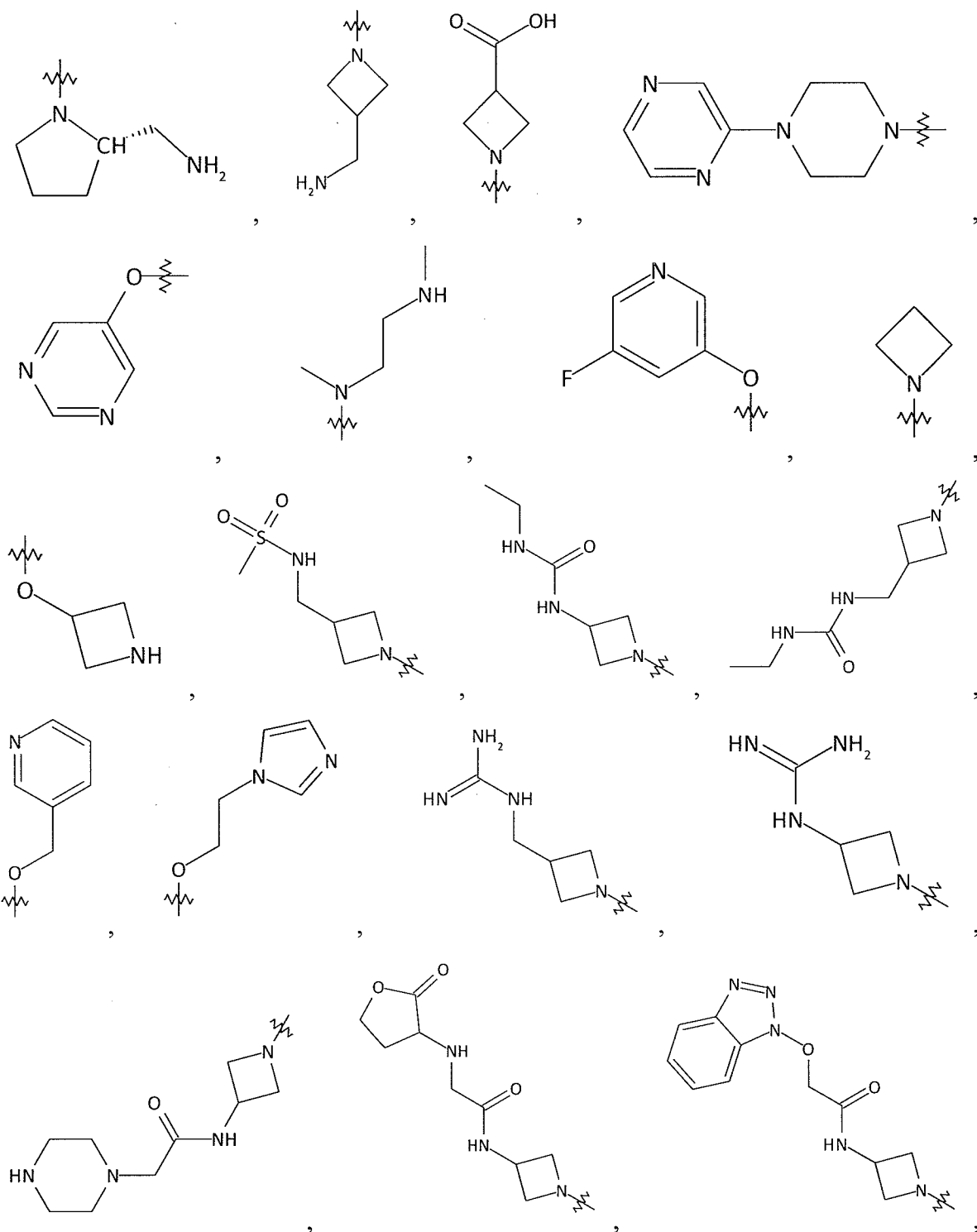


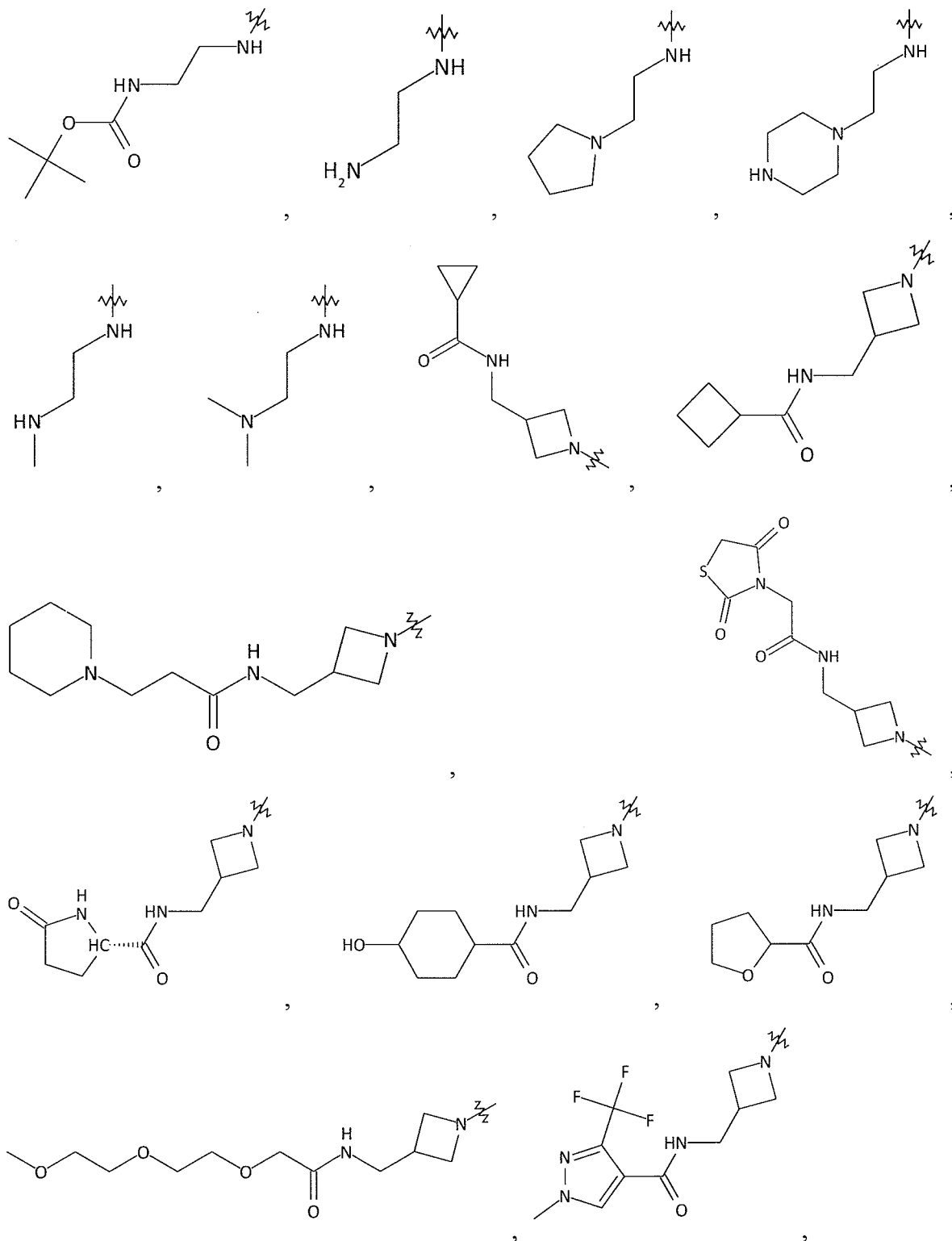


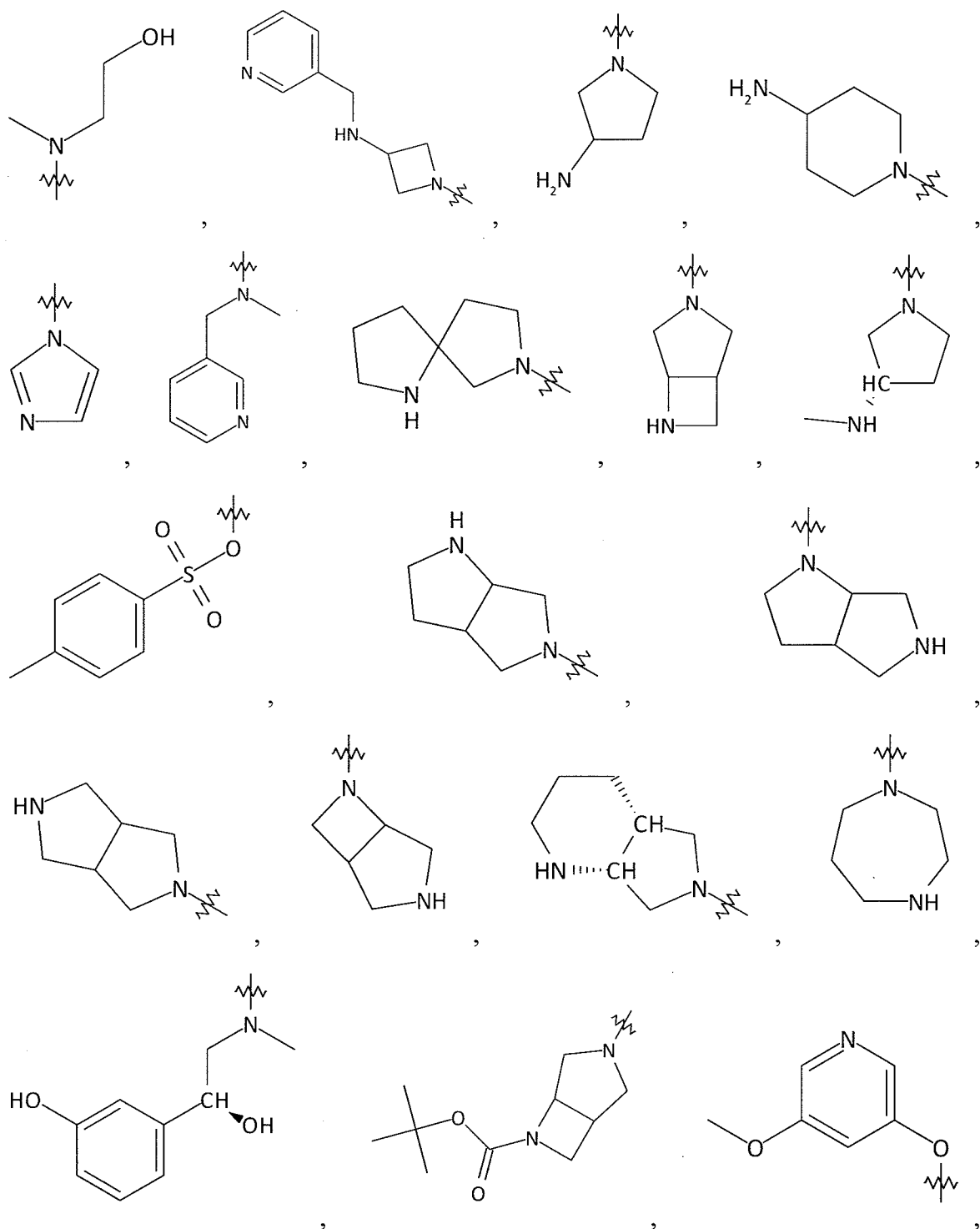


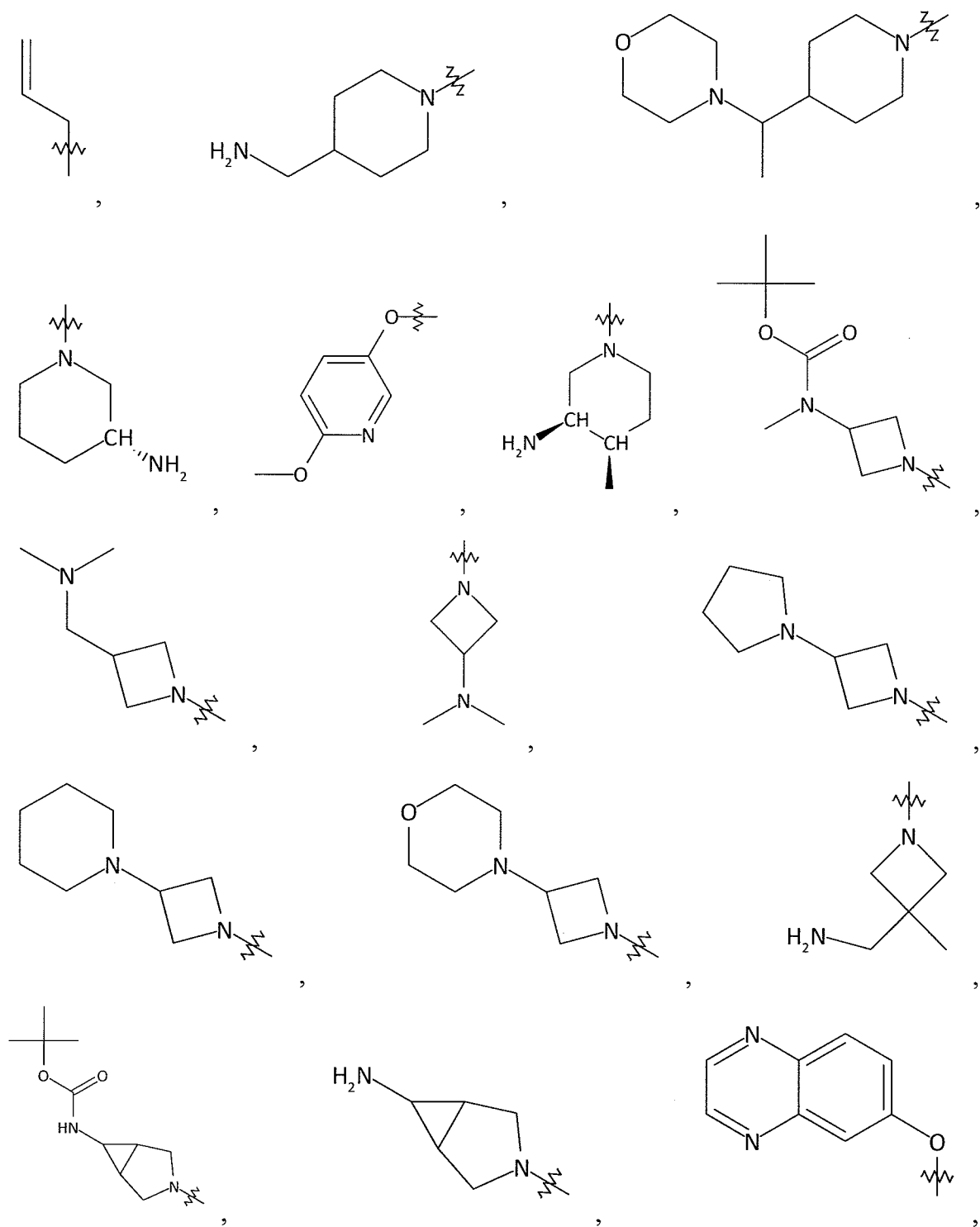


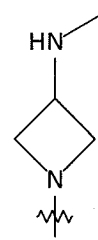
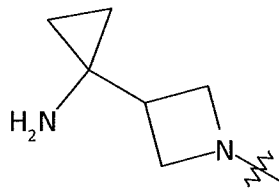
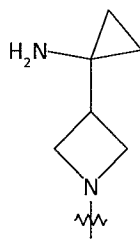
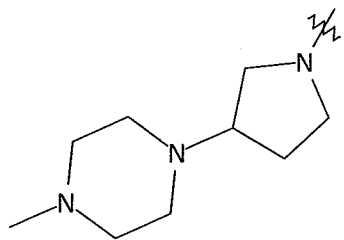
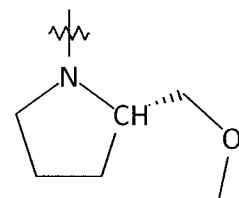
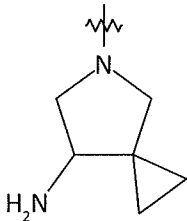
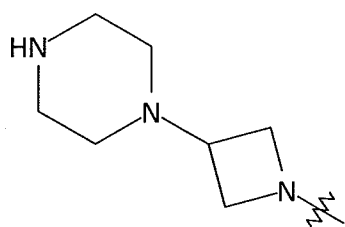
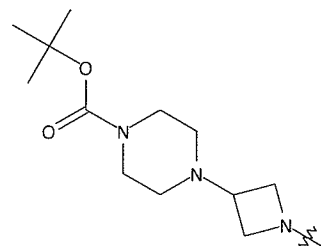
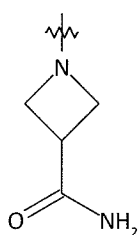
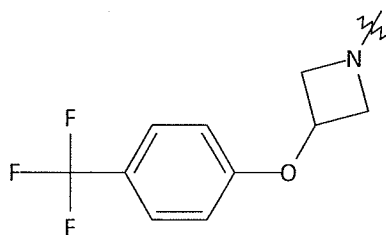
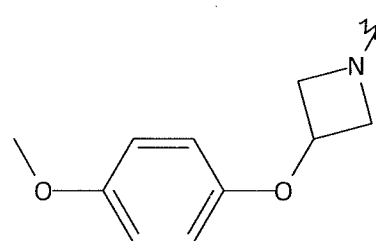
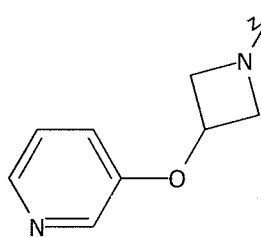
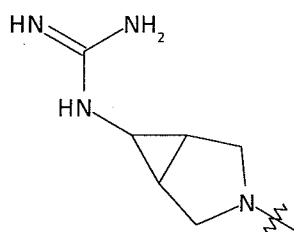
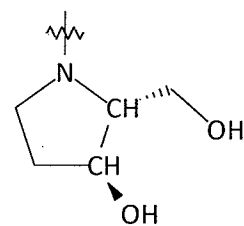
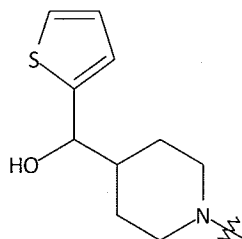
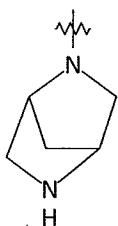
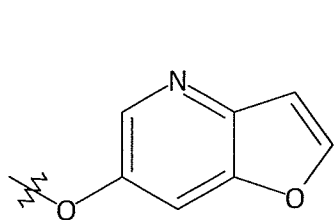
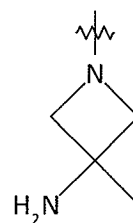
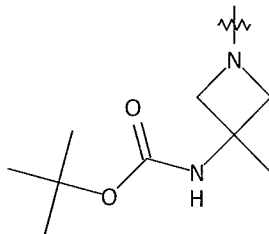
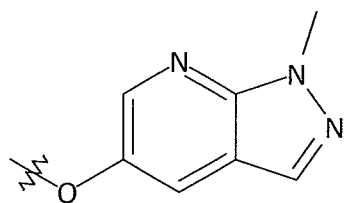


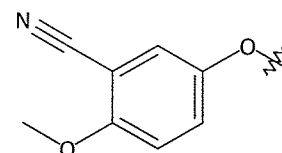
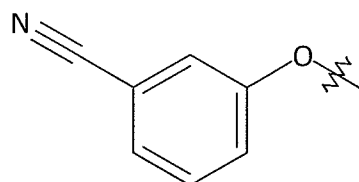
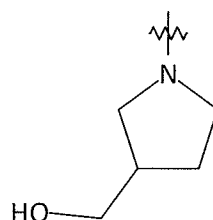
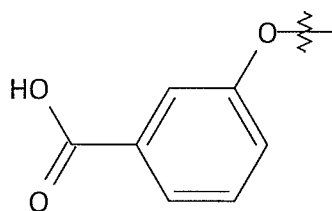
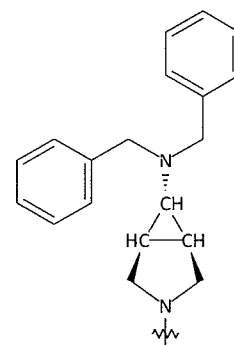
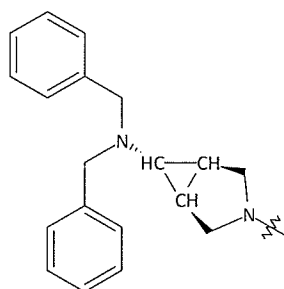
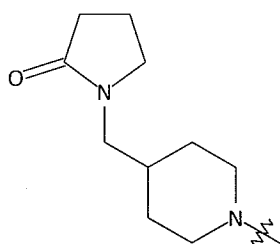
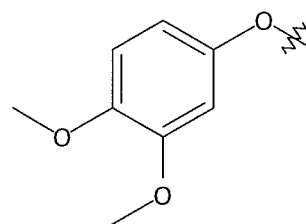
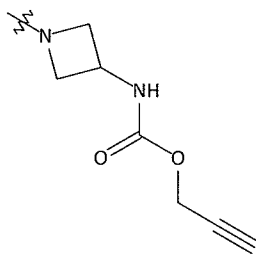
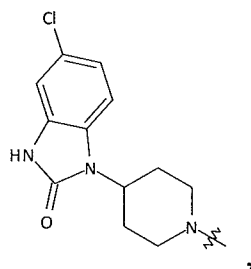
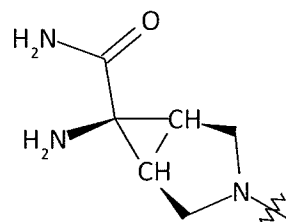
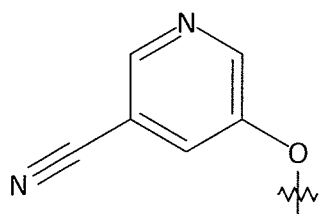
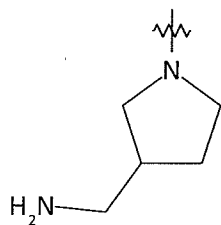


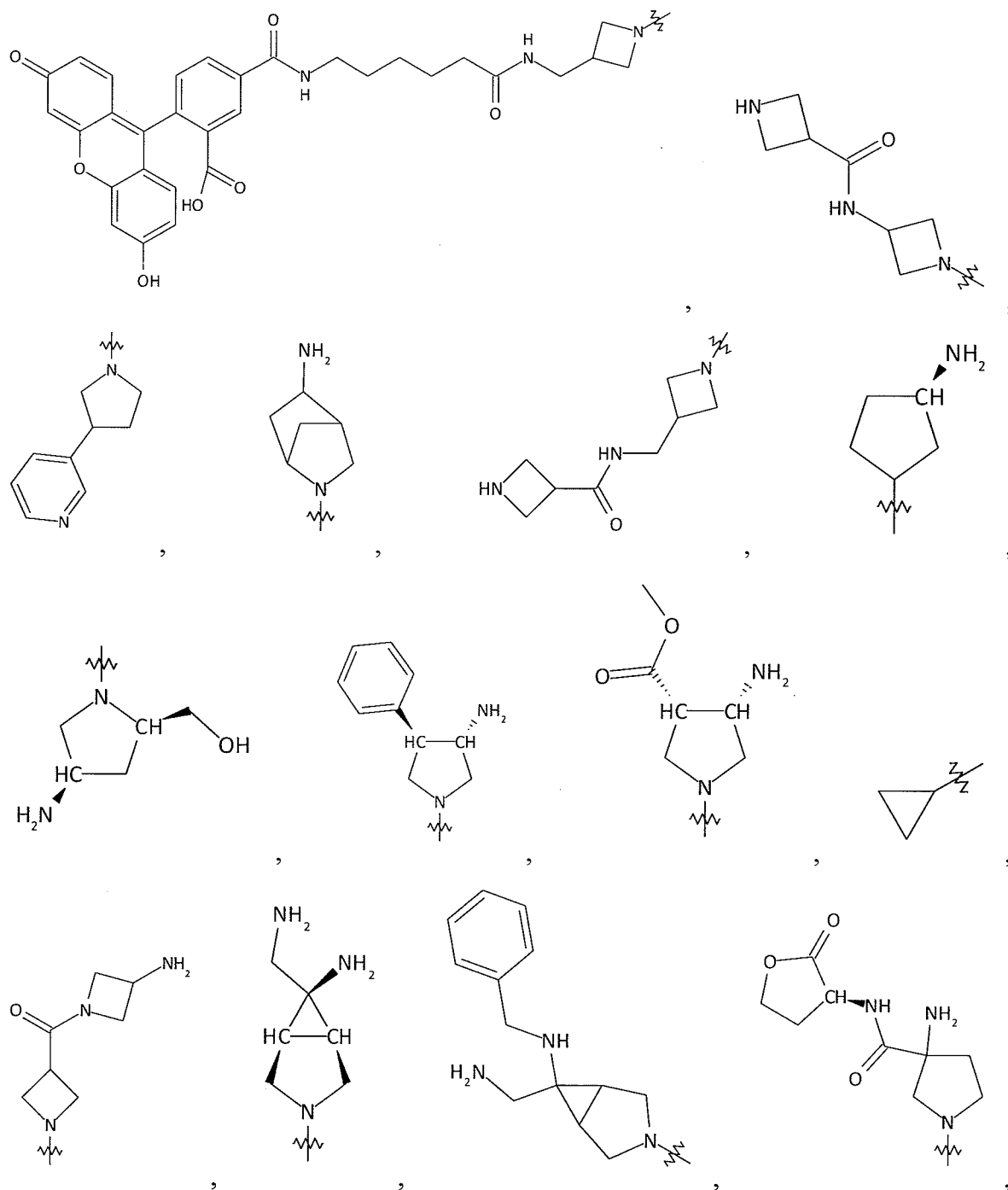


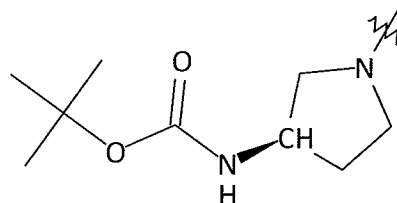
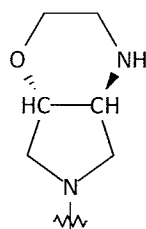
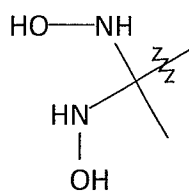
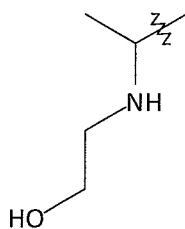
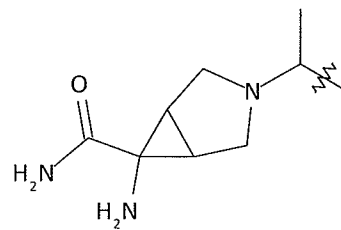
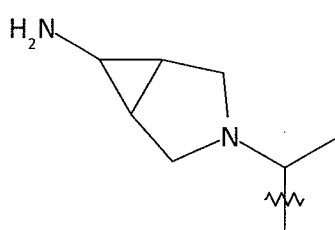
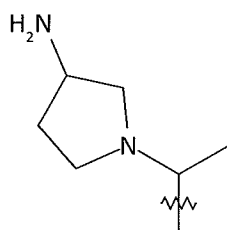
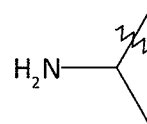
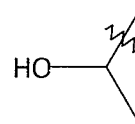
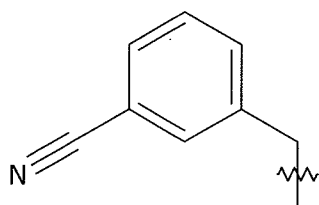
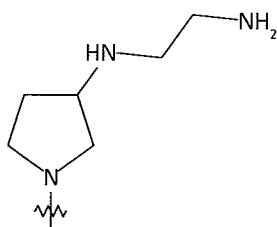
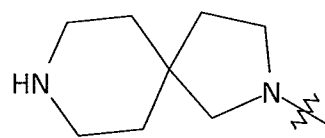
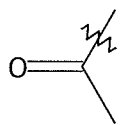
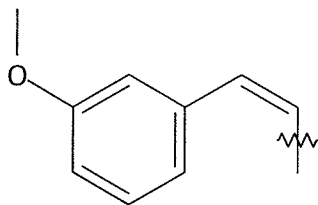
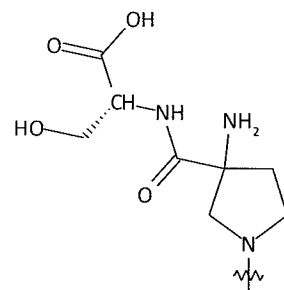
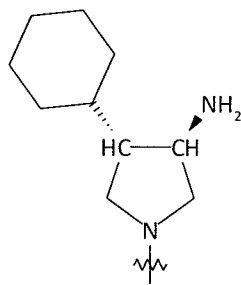
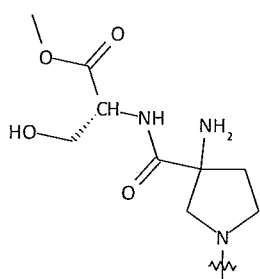


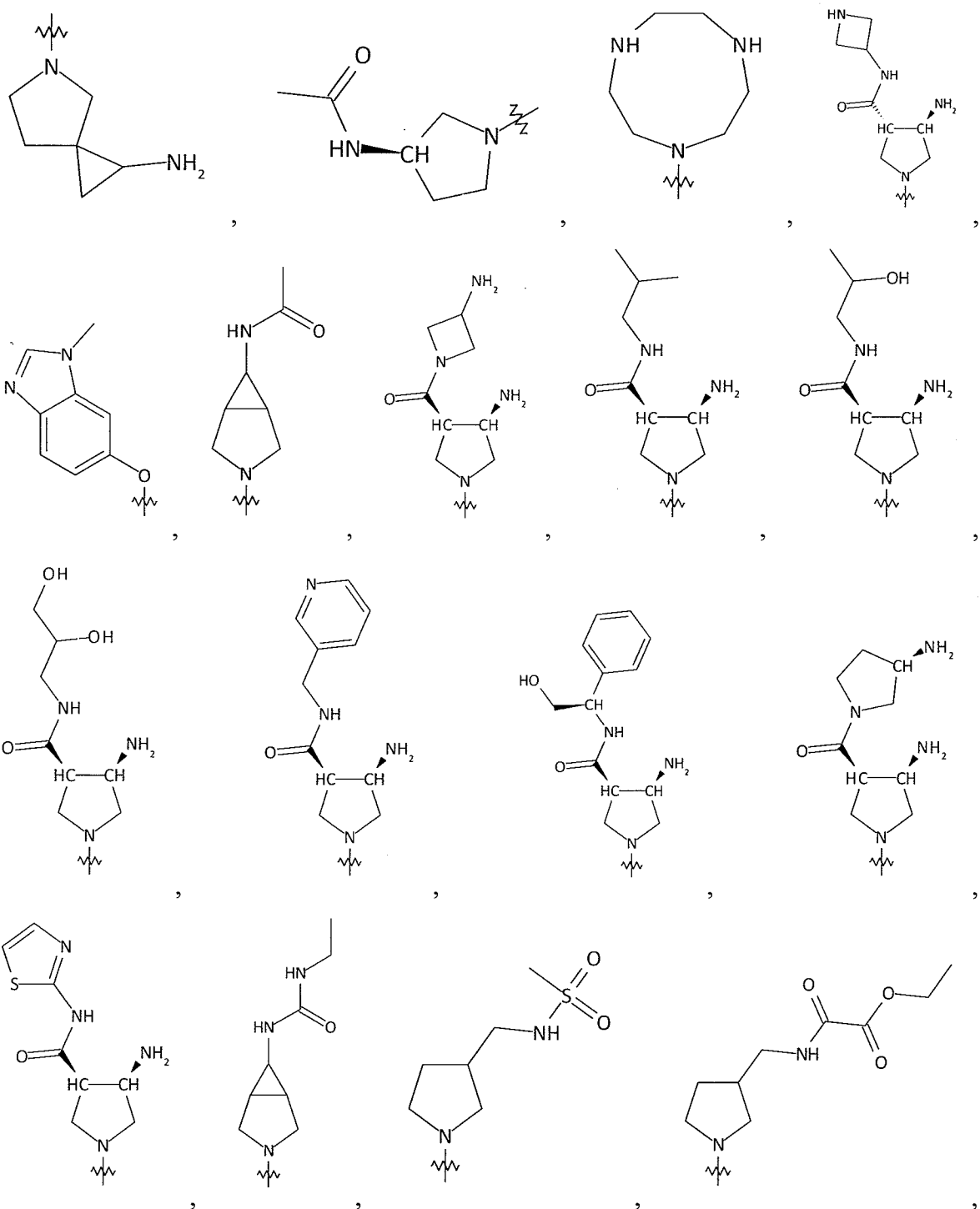


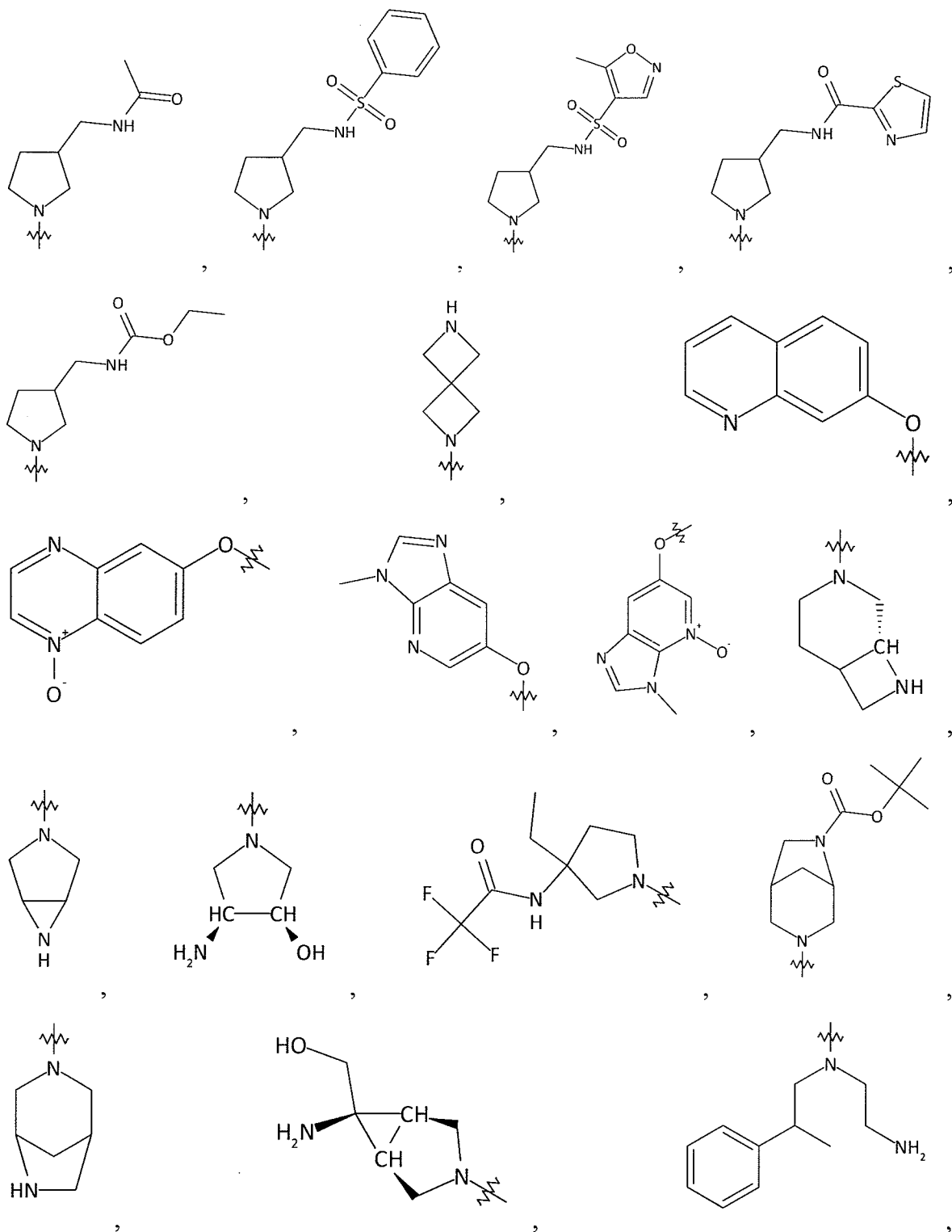


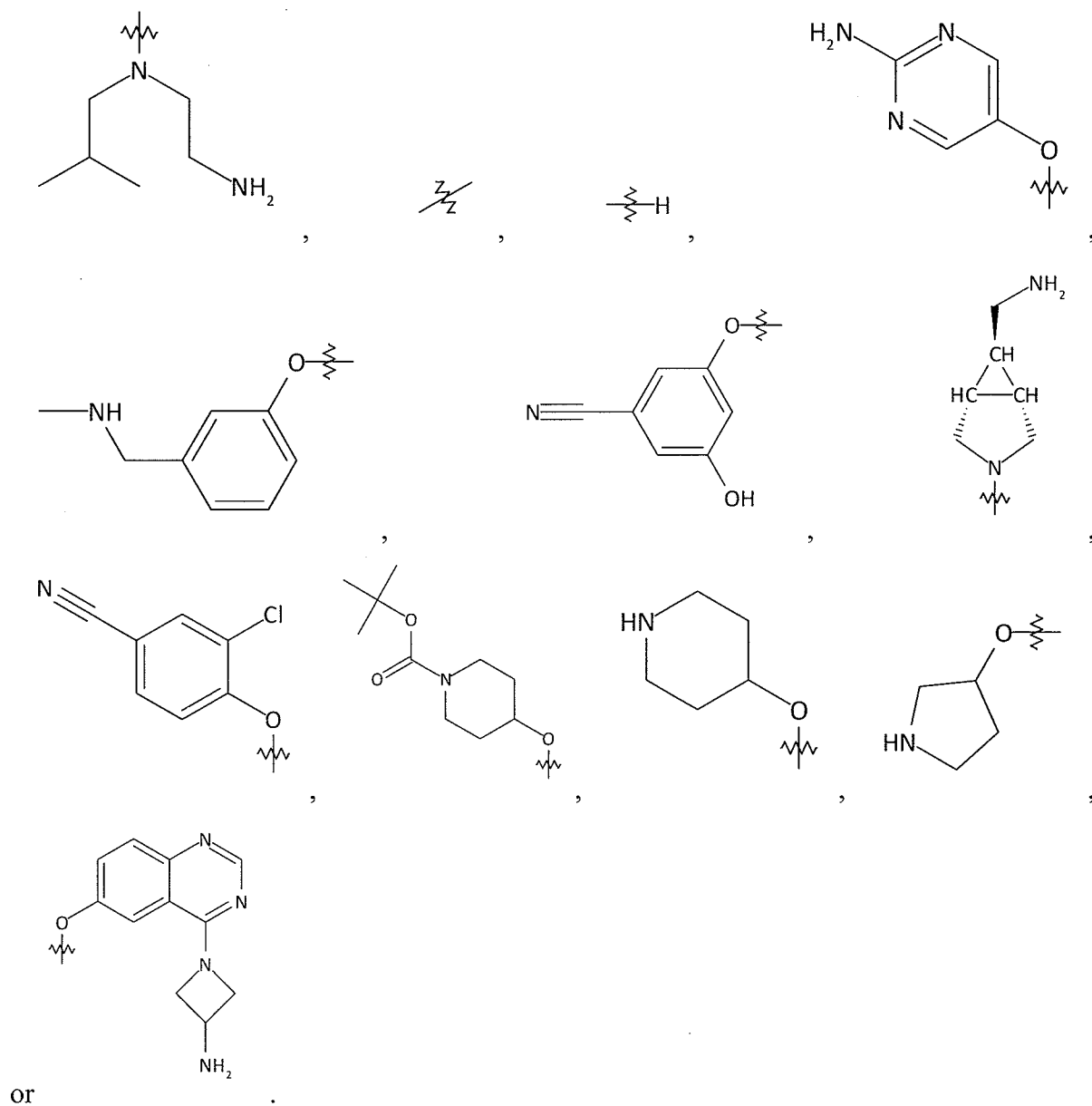












[0025] R^4 may also be selected from the group consisting of optionally-substituted azetidine, pyrrolidine, piperidine, piperazine, and morpholine. In addition, R^4 may be selected from the group consisting azetidin-3-amine, pyrrolidin-3-amine, 3,6-diazabicyclo[3.2.0]heptane, 3-azabicyclo[3.1.0]hexan-6-amine, 1H-pyrrolo[3,4-b]pyridine, octahydropyrrolo[3,4-b]pyrrole, and 2-azabicyclo[2.2.1]heptan-5-amine.

[0026] R^6 may be H, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, halo C_{1-5} alkyl, halo C_{2-5} alkenyl, halo C_{2-5} alkynyl, C_{1-5} hydroxyalkyl, C_{1-5} alkyl chloride, C_{2-5} alkenyl chloride, and C_{2-5} alkynyl chloride. For example, R^6 may be selected from the group consisting of H, Cl, ethyl, vinyl, vinyl chloride, vinyl dichloride, CH_2CH_2OH , $CH(OH)CH_3$, cyclopropyl, CH_2CF_3 , or ethynyl chloride. In some embodiments, R^6 is ethyl.

[0027] In some aspects, R^6 may be Cl, Br, I, Me, Et, CH_2F , CHF_2 , CF_3 , CH_2OH , or 2-chlorovinylidene.

[0028] As used herein, the term "alkyl," "alkenyl" and "alkynyl" include straight- and branched-chain and cyclic monovalent substituents. Examples include methyl, ethyl, isobutyl, cyclopropyl, cyclohexyl, cyclopentylethyl, 2-propenyl, 3-butenyl, and the like. Typically, the alkyl, alkenyl and alkynyl substituents contain 1-15C (alkyl) or 2-10C (alkenyl or alkynyl). They may contain 1-10 or 1-6C (alkyl), or 2-8 or 2-6C (alkenyl or alkynyl). Heteroalkyl, heteroalkenyl and heteroalkynyl are similarly defined but may contain 1-10, such as 1-6, O, S or N heteroatoms or combinations thereof within the backbone residue. Some heteroalkyl, heteroalkenyl and heteroalkynyl contain, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, O, S or N heteroatoms or combinations thereof. The term "alkyl," "alkenyl" or "alkynyl" also includes consecutive ring systems wherein two or more ring systems are spaced by a bond or acyclic alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl and heteroalkynyl. For example, two immediately adjacent cycloalkyl and/or heteroalkyl rings, or two such rings spaced by, for example, alkyl or heteroalkyl. Cyclic substituents encompass fused multiple ring systems including fused bridged rings and spiro systems wherein the cycloalkyl ring or heterocycloalkyl ring has a carbon ring atom in common with another ring.

[0029] "Alicyclic" refers to optionally-substituted cycloalkanes comprising 3-14 carbon atoms in either a monocyclic or, where possible, fused bicyclic arrangement. Alicyclic may have C3-10 or C3-6 carbon atoms. "Heterocyclic" (or "heterocycle") refers to optionally-substituted monocyclic and fused bicyclic non-aromatic groups, saturated or unsaturated, having the specified number of members, containing 1-4 heteroatoms selected from N, O and S. Examples include tetrahydrofuran, dihydropyran, tetrahydropyran, pyran, oxetane, thietane, 1,4-dioxane, 1,3-dioxane, 1,3-dioxalane, piperidine, piperazine,

tetrahydropyrimidine, pyrrolidine, morpholine, thiomorpholine, thiazolidine, oxazolidine, tetrahydrothiopyran, and tetrahydrothiophene.

[0030] "Optionally-substituted" refers to the possible presence of one or more pendant substituents. "Substituted" refers to the presence of one or more pendant substituents in which hydrogen is replaced by a group such as but not restricted to halo, alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkoxy, cycloalkoxy, amino, hydroxy, alkylhydroxy, alkylamine, cycloalkylamine, carboxy, carboxamide, sulfonamide, or heterocyclyl nitrile, alkyl sulfoxide, or thioether. Substituents are discussed herein with respect to various R groups. "Optionally substituted substituent" refers to the possible presence of additional pendant substituents on the first-named substituent, which may be similar to the type of first-named substituent. In some embodiments, substituents that are present are "non-interfering" and thus leave the antibiotic activity of the compound of Formula I qualitatively intact. Thus, the substituent may alter the degree of antibiotic activity. However, as long as the compound of Formula I retains some antibiotic activity, the substituent is considered non-interfering.

"Aryl" refers to optionally-substituted monocyclic and fused bicyclic carbocyclic groups having from five to 12 carbon atoms and having at least one aromatic ring. Examples of particular aryl groups include phenyl and naphthyl.

"Heteroaryl" refers to optionally-substituted aromatic monocyclic and fused bicyclic groups having the specified number of members and containing 1-10 heteroatoms selected from N, O and S. Examples of particular heteroaryl groups include furan, furopyridine, thiophene, pyrrole, imidazole, imidazopyridine, pyrazole, triazole, triazolopyridine, tetrazole, thiazole, thiazolopuridine, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, purine pyridine, pyridopurazine, pyridopyrimidine, pyrazolopyridine, pyridazine, pyrazine, pyrimidine, quinoline, quinoxaline isoquinoline, benzofuran, benzopyran, benzothiophene, benzotriazine, naphthyridine, indole, and indazole.

[0031] Substituents on aryl or heteroaryl may occupy all available positions of the ring, such as 1 or 2 positions, or a single position. The aryl or heteroaryl may be unsubstituted. If substituted, these substituents may be optionally substituted with substituents similar to those listed. Of course some substituents, such as halo, are not further

substituted, as known to one skilled in the art. Two substituents may join and form a fused 3-14 member ring

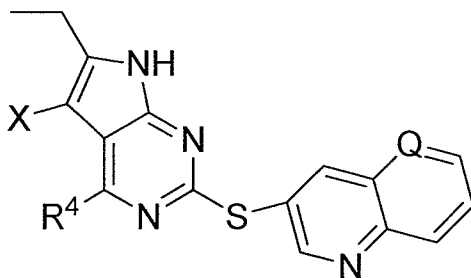
[0032] As used herein, "hydrocarbyl residue" refers to a residue which contains only carbon and hydrogen. The residue may be aliphatic or aromatic, straight-chain, cyclic, branched, saturated or unsaturated. The hydrocarbyl residue, when so stated however, may contain heteroatoms over and above the carbon and hydrogen members of the substituent residue. Thus, when specifically noted as containing such heteroatoms, the hydrocarbyl residue may also contain carbonyl groups, amino groups, sulfonyl groups, nitrile groups, hydroxyl groups and the like, or may contain heteroatoms or groups containing heteroatoms within the "backbone" of the hydrocarbyl residue.

[0033] As used herein, "inorganic residue" refers to a residue that does not contain carbon. Examples include, but are not limited to, halo, hydroxy, NH_2 , SO_2 and the like.

[0034] As used herein, "acyl" encompasses the definitions of alkyl, alkenyl, alkynyl and the related hetero-forms which are coupled to an additional residue through a carbonyl group.

[0035] Similarly, "arylalkyl" and "heteroarylalkyl" contain both aryl and alkyl components, which may contain heteroatoms in either or both components. For example, aromatic and heteroaromatic systems may be coupled to another residue through a carbon chain, including substituted or unsubstituted, saturated or unsaturated, carbon chains, typically of 1-10C, containing 0-5 heteroatoms. These carbon chains may also include a carbonyl group, thus making them able to provide these substituents as acyl moieties. Arylalkenyl and arylalkynyl and hetero forms thereof are similarly defined.

[0036] In some embodiments, the compound of Formula I has the structure of Formula II

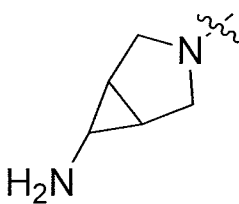
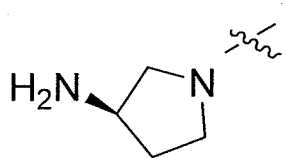


Formula II

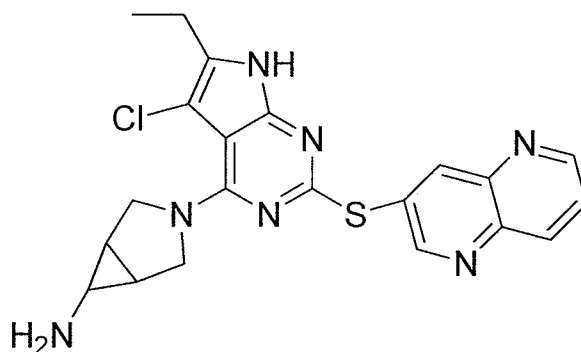
X may be halogen, such as Cl or Br, which in some aspects is Cl.

Q may be N or N⁺-O⁻.

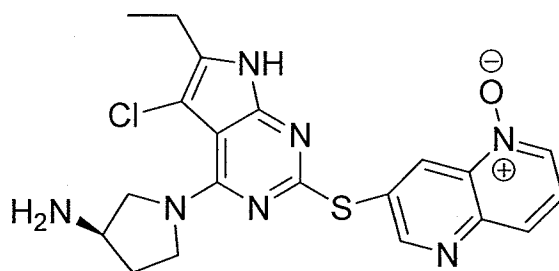
[0037] R⁴ may be an amine-substituted heteroalicyclic ring such as a 4-7 or 5-6 membered heteroalicyclic ring containing an N heteroatom, such as in the backbone of the ring. The heteroalicyclic ring may include a single ring, a fused ring, or a bridged ring

structure. For example, R⁴ may be  or . An amine substituent may be a primary amine such as NH₂, a secondary amine such as NH-alkyl (1-3C) or the tertiary amine such as N-(alkyl (1-3C))₂. In some aspects the 5-6 membered heteroalicyclic ring is substituted with one NH₂, for example, in a position that is not immediately adjacent to the heteroatom such as the N heteroatom in the heteroalicyclic ring.

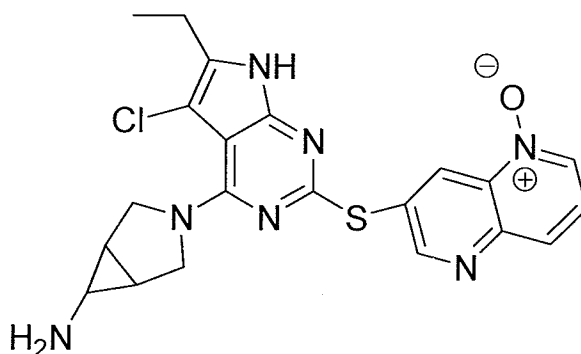
[0038] A compound of Formula II may have the structure:



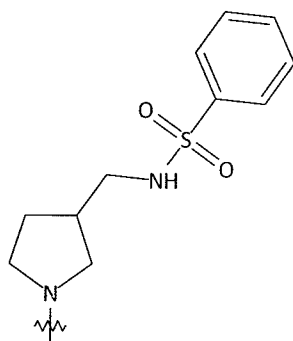
[0039] A compound of Formula II may have the structure:



[0040] A compound of Formula II also may have the structure:



[0041] Groups may be defined in one, two or more ways. For example, the group



may be defined as both a) a heteroalkyl group substituted with $\text{NHSO}_2\text{R}''$, wherein R'' is a aryl, or b) a heteroalkyl group substituted with two $=\text{O}$ (on S) and further substituted with aryl (on S), wherein N and S are in the “backbone” of the heteroalkyl group.

[0042] When the compounds of Formula I and II contain one or more chiral centers, the invention includes optically pure forms as well as mixtures of stereoisomers or enantiomers.

[0043] The term “members” or “membered” in the context of heterocyclic and heteroaryl groups refers to the total atoms, carbon and heteroatoms N, O and/or S, which form the ring. Thus, an example of a 6-membered heterocyclic ring is piperidine and an example of a 6-membered heteroaryl ring is pyridine.

[0044] A pharmaceutically-acceptable salt, ester, or prodrug of the compound of Formula I or II is also contemplated. Those skilled in the art will appreciate that a variety of prodrugs, salts, hydrates, solvates, and polymorphs can be produced from the compounds disclosed here, and that various isotopically-substituted variants (through, e.g., substitution of

deuterium for hydrogen, ^{13}C for carbon, ^{15}N for nitrogen, or ^{32}P for phosphorus) known as "isotopomers" can also be readily produced. All such derivatives are contemplated within the scope of this disclosure.

[0045] Many of the compounds here are disclosed as hydrochloride or other salts, but those skilled in medicinal chemistry will appreciate that the choice of salt is not critical, and other pharmaceutically-acceptable salts can be prepared by well-known methods. Handbook of Pharmaceutical Salts: Properties, Selection and Use. (P. Heinrich Stahl and Camille G. Wermuth, eds.) International Union of Pure and Applied Chemistry, Wiley-VCH 2002 and L.D. Bighley, S.M. Berge, D.C. Monkhouse, in "Encyclopedia of Pharmaceutical Technology". Eds. J. Swarbrick and J.C. Boylan, Vol. 13, Marcel Dekker, Inc., New York, Basel, Hong Kong 1995, pp. 453-499 discuss such salts in detail.

[0046] More generally, those skilled in the art will appreciate that a variety of prodrugs, salts, hydrates, solvates, and polymorphs can be produced from the compounds disclosed here, and that various isotopically-substituted variants (through, e.g., substitution of deuterium for hydrogen, ^{13}C for carbon, ^{15}N for nitrogen) can also be readily produced. All such derivatives are contemplated within the scope of this disclosure.

[0047] Compounds disclosed herein include those structures that are set out in Table 1 appended to the application. In some embodiments, the compound is in a pharmaceutical composition or a dosage form, wherein the pharmaceutical composition or dosage form provides an effective antibiotic-treating or -preventing amount of the compound.

[0048] In another aspect, the present disclosure relates to a pharmaceutical composition comprising one or more physiologically acceptable surface active agents, additional carriers, diluents, excipients, smoothing agents, suspension agents, film forming substances, and coating assistants, or a combination thereof; and a composition disclosed herein. Acceptable additional carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Co., Easton, PA (1990), which is incorporated herein by reference in its entirety. Preservatives, stabilizers, dyes, sweeteners, fragrances, flavoring agents, and the like may be provided in the pharmaceutical composition. For example, sodium benzoate, ascorbic acid and esters of p-hydroxybenzoic acid may be added as preservatives. In

addition, antioxidants and suspending agents may be used. In various embodiments, alcohols, esters, sulfated aliphatic alcohols, and the like may be used as surface active agents; sucrose, glucose, lactose, starch, microcrystalline cellulose, crystallized cellulose, mannitol, light anhydrous silicate, magnesium aluminate, magnesium metasilicate aluminate, synthetic aluminum silicate, calcium carbonate, sodium acid carbonate, calcium hydrogen phosphate, calcium carboxymethyl cellulose, and the like may be used as excipients; magnesium stearate, talc, hardened oil and the like may be used as smoothing agents; coconut oil, olive oil, sesame oil, peanut oil, soya may be used as suspension agents or lubricants; cellulose acetate phthalate as a derivative of a carbohydrate such as cellulose or sugar, or methylacetate-methacrylate copolymer as a derivative of polyvinyl may be used as suspension agents; and plasticizers such as ester phthalates and the like may be used as suspension agents.

[0049] The term “pharmaceutical composition” refers to a mixture of a compound disclosed herein with other chemical components, such as diluents or additional carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a pharmaceutical composition exist in the art including, but not limited to, oral, injection, aerosol, parenteral, and topical administration. Pharmaceutical compositions can also be obtained by reacting the free acid dihydrogen phosphate with inorganic or organic bases such as sodium hydroxide or magnesium hydroxide. In some embodiments, pharmaceutically acceptable salts of the compounds disclosed herein (*e.g.*, as made *in situ* during the manufacture of an intravenous formulation) are provided.

[0050] The term “carrier” refers to a chemical compound that facilitates the incorporation of a compound into cells or tissues.

[0051] The term “diluent” refers to chemical compounds diluted in water that will dissolve the composition of interest as well as stabilize the biologically active form of the compound. Salts dissolved in buffered solutions are utilized as diluents in the art. One commonly used buffered solution is phosphate buffered saline because it mimics the salt conditions of human blood. Since buffer salts can control the pH of a solution at low concentrations, a buffered diluent rarely modifies the biological activity of a compound. As

used herein, an “excipient” refers to an inert substance that is added to a composition to provide, without limitation, bulk, consistency, stability, binding ability, lubrication, disintegrating ability, etc., to the composition. A “diluent” is a type of excipient.

[0052] The term “physiologically acceptable” refers to a carrier or diluent that does not abrogate the biological activity and properties of the compound.

[0053] The pharmaceutical compounds described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredient(s), as in combination therapy, or suitable carriers or excipient(s). In some embodiments, a dosage form includes those forms in which the compound is administered *per se*. In addition, a dosage form may include a pharmaceutical composition. In any case, the dosage form may comprise a sufficient amount of the dimer compound to treat a bacterial infection as part of a particular administration protocol, as would be understood by those of skill in the art. Techniques for formulation and administration of the compounds of the instant application may be found in “Remington’s Pharmaceutical Sciences,” Mack Publishing Co., Easton, PA, 18th edition, 1990.

[0054] Suitable routes of administration may, for example, include oral, rectal, transmucosal, topical, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections. The compound can also be administered in sustained or controlled release dosage forms, including depot injections, osmotic pumps, pills, transdermal (including electrotransport) patches, and the like, for prolonged and/or timed, pulsed administration at a predetermined rate.

[0055] The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes.

[0056] Pharmaceutical compositions may be formulated in any conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration

chosen. Any of the well-known techniques, diluents, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences, above.

[0057] Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, mannitol, lactose, lecithin, albumin, sodium glutamate, cysteine hydrochloride, and the like. In addition, if desired, the injectable pharmaceutical compositions may contain minor amounts of nontoxic auxiliary substances, such as wetting agents, pH buffering agents, and the like. Physiologically compatible buffers include, but are not limited to, Hanks's solution, Ringer's solution, or physiological saline buffer. If desired, absorption enhancing preparations may be utilized.

[0058] For transmucosal administration, penetrants appropriate to the barrier to be permeated may be used in the formulation.

[0059] Pharmaceutical formulations for parenteral administration, *e.g.*, by bolus injection or continuous infusion, include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[0060] For oral administration, the composition can be formulated readily by combining the compositions of interest with pharmaceutically acceptable carriers well known in the art. Such carriers, which may be used in addition to the cationic polymeric carrier, enable the compositions of the invention to be formulated as tablets, pills, dragees, capsules,

liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by combining the active compound with solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP), *e.g.*, Povidone. If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone (*e.g.* Crospovidone), agar, or alginic acid or a salt thereof such as sodium alginate. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0061] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

[0062] For buccal administration, the compositions may take the form of tablets or lozenges formulated in a conventional manner.

[0063] For administration by inhalation, the composition can be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized

aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0064] Further disclosed herein are various pharmaceutical compositions well known in the pharmaceutical art for uses that include intraocular, intranasal, and intraauricular delivery. Suitable penetrants for these uses are generally known in the art. Such suitable pharmaceutical formulations are most often and preferably formulated to be sterile, isotonic and buffered for stability and comfort. Pharmaceutical compositions for intranasal delivery may also include drops and sprays often prepared to simulate in many respects nasal secretions to ensure maintenance of normal ciliary action. As disclosed in Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Co., Easton, PA (1990), which is incorporated herein by reference in its entirety, and well-known to those skilled in the art, suitable formulations are most often and preferably isotonic, slightly buffered to maintain a pH of 5.5 to 6.5, and most often and preferably include antimicrobial preservatives and appropriate drug stabilizers. Pharmaceutical formulations for intraauricular delivery include suspensions and ointments for topical application in the ear. Common solvents for such aural formulations include glycerin and water.

[0065] The compositions may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

[0066] In addition to the formulations described previously, the compositions may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0067] For hydrophobic compounds, a suitable pharmaceutical carrier may be a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. A common cosolvent system used is the VPD co-solvent

system, which is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of POLYSORBATE 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

[0068] Methods for treating bacterial infections may include administering a therapeutically effective amount of the therapeutic compounds as described herein. Treating a bacterial infection may also include prophylactically administering the therapeutic compounds to prevent infection or the spread of an infection in a subject at imminent risk of infection, such as a subject receiving or about to undergo surgery, an immunocompromised subject, or subject otherwise at risk of an infection if the compound was not administered. The compounds show inhibitory activity against a broad spectrum of bacteria including *H. influenzae*, *E. coli*, *S. aureus*, *A. baumannii*, *S. pneumoniae*, *P. aeruginosa*, and *B. thailandensis*, for example methicillin resistant *Staphylococcus aureus* (MRSA). See **Table 2**. The compounds have excellent relative antibiotic activity with a relatively low concentration. Further, the compounds of the present invention may exert potent antibacterial activity versus various human and animal pathogens, including Gram-positive and Gram-negative bacteria. In an embodiment, the bacterial infection that may be treated or ameliorated is MRSA.

[0069] The compositions or pharmaceutical compositions described herein may be administered to the subject by any suitable means. Non-limiting examples of methods of administration include, among others, (a) administration through oral pathways, which administration includes administration in capsule, tablet, granule, spray, syrup, or other such forms; (b) administration through non-oral pathways such as rectal, vaginal, intraurethral, intraocular, intranasal, or intraauricular, which administration includes administration as an aqueous suspension, an oily preparation or the like or as a drip, spray, suppository, salve, ointment or the like; (c) administration via injection, subcutaneously, intraperitoneally,

intravenously, intramuscularly, intradermally, intraorbitally, intracapsularly, intraspinally, intrasternally, or the like, including infusion pump delivery; as well as (d) administration topically; as deemed appropriate by those of skill in the art for bringing the active compound into contact with living tissue.

[0070] Pharmaceutical compositions suitable for administration include compositions where the active ingredients are contained in an amount effective to achieve its intended purpose. In some embodiments, a therapeutically effective amount of a compound is an amount effective to treat a bacterial infection, for example, in a mammalian subject (*e.g.*, a human). The therapeutically effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated, and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize. More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0071] As will be readily apparent to one skilled in the art, the useful *in vivo* dosage to be administered and the particular mode of administration will vary depending upon the age, weight and mammalian species treated, the particular compounds employed, and the specific use for which these compounds are employed. The determination of effective dosage levels, that is the dosage levels necessary to achieve the desired result, can be accomplished by one skilled in the art using routine pharmacological methods. Typically, human clinical applications of products are commenced at lower dosage levels, with dosage level being increased until the desired effect is achieved. Alternatively, acceptable *in vitro* studies can be used to establish useful doses and routes of administration of the compositions identified by the present methods using established pharmacological methods.

[0072] In non-human animal studies, applications of potential products are commenced at higher dosage levels, with dosage being decreased until the desired effect is no

longer achieved adverse side effects disappear. The dosage may range broadly, depending upon the desired effects and the therapeutic indication. Typically, dosages may be about 10 microgram/kg to about 100 mg/kg body weight, preferably about 100 microgram/kg to about 10 mg/kg body weight. Alternatively dosages may be based and calculated upon the surface area of the patient, as understood by those of skill in the art.

[0073] The exact formulation, route of administration and dosage for the pharmaceutical compositions of the present invention can be chosen by the individual physician in view of the patient's condition. (See *e.g.*, Fingl et al. 1975, in "The Pharmacological Basis of Therapeutics", which is hereby incorporated herein by reference in its entirety, with particular reference to Ch. 1, p. 1). In some embodiments, the dose range of the composition administered to the patient can be from about 0.5 to about 1000 mg/kg of the patient's body weight. The dosage may be a single one or a series of two or more given in the course of one or more days, as is needed by the patient. In instances where human dosages for compounds have been established for at least some condition, the present invention will use those same dosages, or dosages that are about 0.1% to about 500%, more preferably about 25% to about 250% of the established human dosage. Where no human dosage is established, as will be the case for newly-discovered pharmaceutical compositions, a suitable human dosage can be inferred from ED₅₀ or ID₅₀ values, or other appropriate values derived from *in vitro* or *in vivo* studies, as qualified by toxicity studies and efficacy studies in animals.

[0074] It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity or organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administered dose in the management of the disorder of interest will vary with the severity of the condition to be treated and to the route of administration. The severity of the condition may, for example, be evaluated, in part, by standard prognostic evaluation methods. Further, the dose and perhaps dose frequency will also vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

[0075] Although the exact dosage will be determined on a drug-by-drug basis, in most cases, some generalizations regarding the dosage can be made. The daily dosage regimen for an adult human patient may be, for example, an oral dose of about 0.1 mg to 2000 mg of the active ingredient, preferably about 1 mg to about 500 mg, *e.g.* 5 to 200 mg. In other embodiments, an intravenous, subcutaneous, or intramuscular dose of the active ingredient of about 0.01 mg to about 100 mg, preferably about 0.1 mg to about 60 mg, *e.g.* about 1 to about 40 mg is used. In cases of administration of a pharmaceutically acceptable salt, dosages may be calculated as the free acid. In some embodiments, the composition is administered 1 to 4 times per day. Alternatively the compositions of the invention may be administered by continuous intravenous infusion, preferably at a dose of up to about 1000 mg per day. As will be understood by those of skill in the art, in certain situations it may be necessary to administer the compounds disclosed herein in amounts that exceed, or even far exceed, the above-stated, preferred dosage range in order to effectively and aggressively treat particularly aggressive diseases or infections. In some embodiments, the compounds will be administered for a period of continuous therapy, for example for a week or more, or for months or years.

[0076] Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the antibiotic effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vitro* data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

[0077] Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

[0078] In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

[0079] The amount of composition administered may be dependent on the subject being treated, on the subject's weight, the severity of the infection, the manner of administration and the judgment of the prescribing physician.

[0080] Compositions disclosed herein can be evaluated for efficacy and toxicity using known methods. For example, the toxicology of the compound may be established by determining *in vitro* toxicity towards a cell line, such as a mammalian, and preferably human, cell line. The results of such studies are often predictive of toxicity in animals, such as mammals, or more specifically, humans. Alternatively, the toxicity of particular compounds in an animal model, such as mice, rats, rabbits, or monkeys, may be determined using known methods. The efficacy of a particular compound may be established using several recognized methods, such as *in vitro* methods, animal models, or human clinical trials. Recognized *in vitro* models exist for nearly every class of condition. Similarly, acceptable animal models may be used to establish efficacy of chemicals to treat such conditions. When selecting a model to determine efficacy, the skilled artisan can be guided by the state of the art to choose an appropriate model, dose, and route of administration, and regime. Of course, human clinical trials can also be used to determine the efficacy of a compound in humans.

[0081] The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

[0082] In some embodiments, in the pharmaceutical industry, it standard practice to provide substantially pure material when formulating pharmaceutical compositions. Therefore, in some embodiments, “substantially pure” refers to the amount of purity required for formulating pharmaceuticals, which may include, for example, a small amount of other material that will not affects the suitability for pharmaceutical use. In some embodiments,

the substantially pure compound contains at least about 96% of the compound by weight, such as at least about 97%, 98%, 99%, or 100% of the compound.

[0083] The terms “approximately,” “about,” and “substantially” as used herein represent an amount close to the stated amount that still performs the desired function or achieves the desired result. For example, the terms “approximately,” “about” and “substantially” may refer to an amount that is within less than 10% of, within less than 5% of, within less than 1% of, within less than 0.1% of, and within less than 0.01% of the stated amount.

Methods of Making the compounds

[0084] As shown in the Examples below, similar methods may be used to make various groups of compounds. In many cases, the final step includes deprotecting a protected form of a compound of Formula I or II wherein Z is C-halo. Protecting groups are well known in the art and include, for example, BOC. In some aspects the final or penultimate step includes halogenating a protected form of the compound of Formula I or II wherein Z is CH to form a compound of Formula I or II wherein Z is C-halo

[0085] Other steps may include before the halogenating step, aminating a compound of Formula I or II wherein Z is CH and R⁴ is OH, or a protected form thereof, to form a compound of Formula I or II wherein R⁴ is a group comprising an amine.

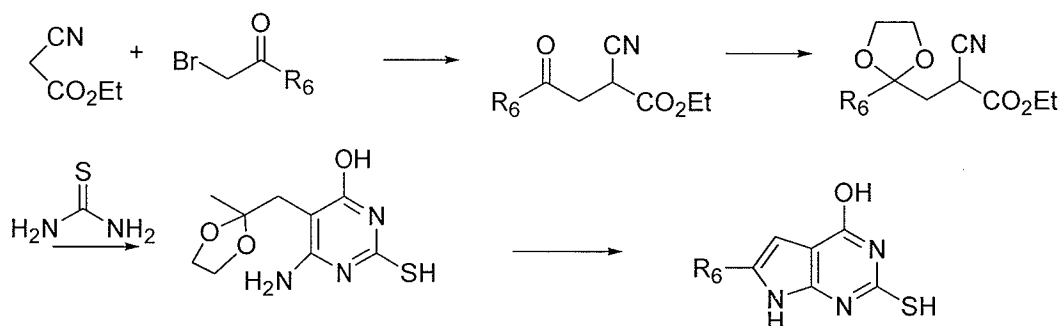
[0086] Other steps include, such as before the aminating step, adding an aryl or heteroaryl to a compound of Formula I or II wherein R₂ is H to form a compound of Formula I or II wherein R₂ is a group comprising an aryl or heteroaryl group directly linked to L.

[0087] In addition to the compounds discussed herein, the Examples also include methods for making various intermediates useful in making the compounds.

EXAMPLES

Preparation of compounds

[0088] The 2-mercapto-7H-pyrrolo[2,3-d]pyrimidine intermediates can be prepared as shown in the following scheme and illustrated in Examples 1-3, where R⁶ = ethyl.



EXAMPLE 1

6-Amino-5-((2-ethyl-1,3-dioxolan-2-yl)methyl)-2-mercaptopyrimidin-4-ol

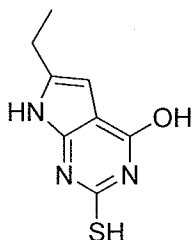
[0089] Ethyl cyanoacetate (35 mL, 331 mmol) was dissolved in toluene (1.5 L) and DBU (50 mL, 331 mmol) was added via dropping funnel. The reaction was allowed to stir for 30 minutes. The pot was placed in an ice bath and allowed to cool to 0°C followed by dropwise addition of 1-bromo-2-butanone (50 g, 331 mmol). This reaction was slightly exothermic so it was monitored and the temperature was not allowed to rise over 10°C. Once addition was complete the reaction turned a brown color. It was allowed slowly warm to room temperature and to react overnight. The next morning the reaction was poured into a separatory funnel and washed 2x with 1 M HCl and 1x with brine. The organic layer was dried with sodium sulfate and filtered. The toluene was removed by rotary evaporator to yield 50 grams of a dark brown liquid. The product was pure as determined by NMR and was carried on to the next step.

[0090] The product, ethyl 2-cyano-4-oxohexanoate, (50 g, 273 mmol) was dissolved in benzene (550 mL). To this solution was added ethylene glycol (22.8 mL, 409 mmol) and p-toluenesulfonic acid monohydrate (1 g, 5.46 mmol). The reaction was equipped with a Dean-Stark trap, a heating mantle and a reflux condenser and the reaction was heated to reflux until the appropriate amount of water was removed from the reaction, anywhere from 2-12 h. The reaction was cooled and poured into a separatory funnel and washed 2x with 10% sodium carbonate and 1x with brine. The organic layer was dried with sodium sulfate, filtered and the solvent removed by rotary evaporator to yield a dark oil. NMR indicated this product was about >90% pure therefore we used it for the next step without further purification.

[0091] Thiourea (20.1 g, 264 mmol) was suspended in dry ethanol (400 mL) and sodium ethoxide (21% solution) (100 mL, 264 mmol) was added. To this reaction was added ethyl 2-cyano-3-(2-ethyl-1,3-dioxolan-2-yl)propanoate (60 g, 264 mmol). The reaction was equipped with a mechanical stirrer, a heating mantle and a reflux condenser and heated to reflux for 6 h during which a precipitate was observed. The next morning the solvent was removed and water (300 mL) was added to the crude product followed by addition of 10% citric acid to pH 7. The solid was collected and the wet cake was washed with cold ethanol to remove most of the brown discoloration. The cake was dried in a vacuum oven overnight to yield the desired amino pyrimidine. The product was used without further purification.

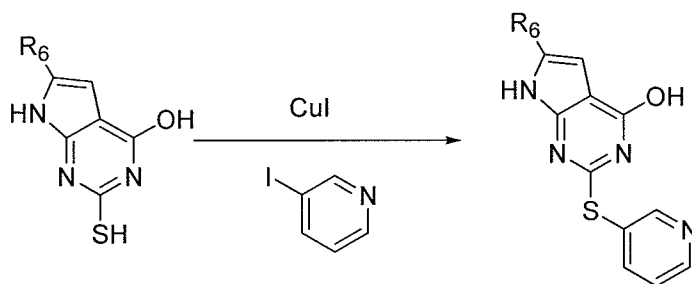
EXAMPLE 2

6-Ethyl-2-mercapto-7H-pyrrolo[2,3-d]pyrimidin-4-ol



[0092] 6-Amino-5-((2-ethyl-1,3-dioxolan-2-yl)methyl)-2-mercaptopyrimidin-4-ol (Example 1) (55 g) was added to THF (200 mL) and to this suspension was added 1 M HCl in water (200 mL). The pyrimidine slowly dissolved in this solution over a 1 h period and a new precipitate formed. The reaction was allowed to proceed overnight and the next day the precipitate was collect via filtration. The filter cake was washed with water and dried in a vacuum oven overnight.

[0093] 2-Mercapto-7H-pyrrolo[2,3-d]pyrimidine intermediates can be readily converted into 2-arylthio-7H-pyrrolo[2,3-d]pyrimidines by copper catalyzed coupling with aryl halides as shown in Example 3.

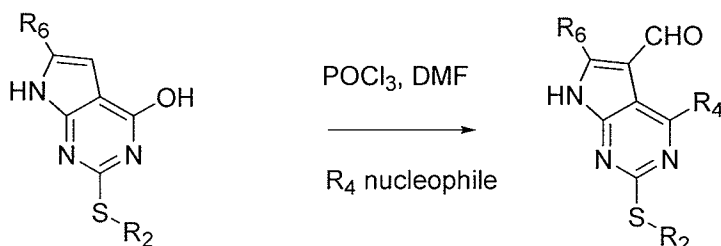


EXAMPLE 3

6-Ethyl-2-(pyridin-3-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-ol

[0094] 6-Ethyl-2-mercapto-7H-pyrrolo[2,3-d]pyrimidin-4-ol (Example 2) (10 g, 51.2 mmol) was combined with potassium carbonate (21.24 g, 154 mmol), 3-iodopyridine (10.5 g, 51.2 mmol), copper iodide (0.488 g, 2.56 mmol), and NMP (256 mL). The reaction was purged of oxygen with a dry stream of nitrogen followed by the addition of ethylene glycol (5.71 mL, 102 mmol). The reaction was heated to 145°C and followed by LCMS. After 6 h the NMP was removed by rotary evaporator and water (200 mL) was added followed by adjusting the pH to neutral using 1 M HCl. The solids were collected. Washed 4x with 100 mL water and 2x with 50 mL of ethyl ether. The precipitate was dried in a vacuum oven overnight and used without further purification.

[0095] Conversion of 2-arylthio-7H-pyrrolo[2,3-d]pyrimidines into compounds of Formula I where $Z = CR^5$ and $R^5 = CHO$ is accomplished using the Vilsmeier-Haack formulation / chlorination followed by the nucleophilic addition of the R^4 group (both $R^4 =$ optionally substituted O and $R^4 =$ optionally substituted N) as shown in Examples 4-6.



EXAMPLE 4

4-Chloro-6-ethyl-2-(pyridin-3-ylthio)-7H-pyrrolo[2,3-d]pyrimidine-5-carbaldehyde

[0096] N,N-dimethylformamide (1 mL) was dissolved in phosphorous oxychloride (120 mL). 6-Ethyl-2-(pyridin-3-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-ol (Example 3) was slowly added to the reaction pot and heated to 105°C for 3 h. The phosphorous oxychloride was removed by rotary evaporator and the remaining syrup was carefully poured syrup on 500 mL of chipped ice. The precipitate was collected and washed with water and dried in a vacuum oven overnight.

EXAMPLE 5

4-Ethoxy-6-ethyl-2-(pyridin-3-ylthio)-7H-pyrrolo[2,3-d]pyrimidine-5-carbaldehyde

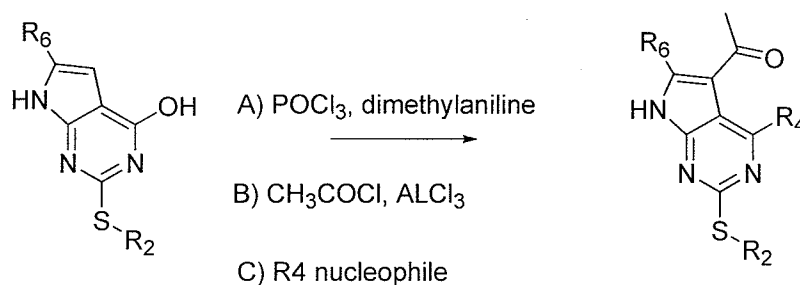
[0097] 4-Chloro-6-ethyl-2-(pyridin-3-ylthio)-7H-pyrrolo[2,3-d]pyrimidine-5-carbaldehyde (Example 4) (0.020 g) was dissolved in ethanol (2 mL) and sodium hydride (0.020 g) was added to the solution followed by heating in a sealed tube at 150°C for 10 min. Compound 8 was purified by reverse phase high performance liquid chromatography (HPLC).

EXAMPLE 6

4-(dimethylamino)-6-ethyl-2-(pyridin-3-ylthio)-7H-pyrrolo[2,3-d]pyrimidine-5-carbaldehyde

[0098] 4-Chloro-6-ethyl-2-(pyridin-3-ylthio)-7H-pyrrolo[2,3-d]pyrimidine-5-carbaldehyde (Example 4) (0.020 g) was dissolved in NMP (1 mL) and a solution of dimethylamine (2 mL) in THF was added. The reaction was heated to 150°C for 10 minutes followed by purification of the desired product by RF-HPLC.

[0099] In cases where compounds of Formula I where $Z = CR^5$ and $R^5 = COCH_3$ can be prepared as shown below in Examples 7-9



EXAMPLE 7

4-chloro-6-ethyl-2-(pyridin-3-ylthio)-7H-pyrrolo[2,3-d]pyrimidine

[0100] 6-ethyl-2-(pyridin-3-ylsulfanyl)-5H-pyrrolo[2,3-d]pyrimidin-4-ol (13 g, 47.7 mmol) (Example 3) was dissolved in phosphorous oxychloride (150 mL) and N, N-dimethylaniline (1 mL, 8 mmol) was added to the solution. The reaction was heated to 105 C for 3 h at which LCMS analysis indicated the reaction was complete. The solvent was removed by rotary evaporator and the syrup was carefully poured on 500 mL chipped ice. After all the ice melted the precipitate was collected by filtration and dried under vacuum overnight.

EXAMPLE 8

1-(4-chloro-6-ethyl-2-(pyridin-3-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethanone

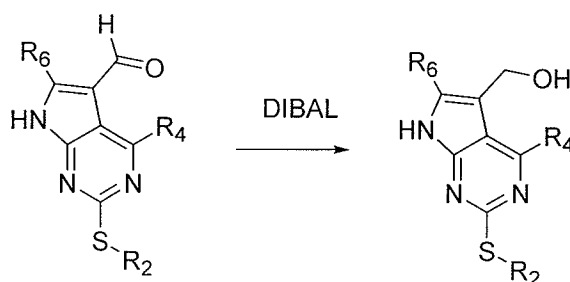
[0101] 4-chloro-6-ethyl-2-(pyridin-3-ylthio)-7H-pyrrolo[2,3-d]pyrimidine (Example 7) (0.2 g, 0.69 mmol), aluminum chloride (0.642 g, 4.8 mmol) was dissolved in dichloromethane (5 mL) and allowed to stir at room temperature for 1 hour. Acetyl chloride (0.050 mL, 0.688 mmol) was added in one aliquot. The reaction was stirred at room temperature for 6 h and poured on ice chips to quench the reaction. Aqueous extraction provided the desired compound which was used without further purification.

EXAMPLE 9

1-(4-ethoxy-6-ethyl-2-(pyridin-3-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethanone

[0102] 1-(4-chloro-6-ethyl-2-(pyridin-3-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethanone (Example 8) (0.050 g, 0.150 mmol) was dissolved in 2 mL of ethanol. To this reaction mixture was added excess sodium hydride. The reaction was heated to 150°C for 10 minutes followed by purification of the desired product by RF-HPLC.

[0103] In cases where compounds of Formula I where $Z = CR^5$ and $R^5 = CH_2OH$ can be prepared as shown below in Example 10.

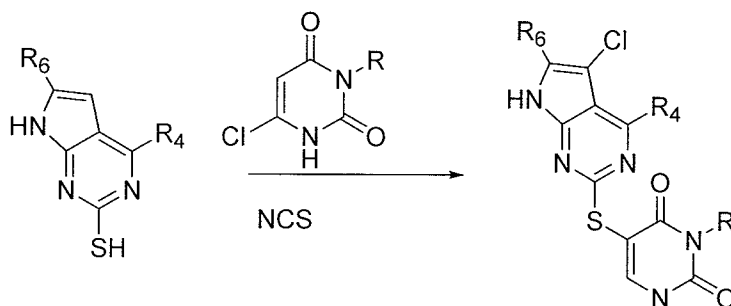


EXAMPLE 10

(S)-1-(6-ethyl-5-(hydroxymethyl)-2-(pyridin-3-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)propan-2-ol (compound 700139)

(S)-6-ethyl-4-(2-hydroxypropylamino)-2-(pyridin-3-ylthio)-7H-pyrrolo[2,3-d]pyrimidine-5-carbaldehyde (0.050 g, 0.14 mmol) was dissolved in THF and diisobutylaluminum hydride in THF (2 mL, 2 mmol). The reaction was allowed to proceed for 2 h and quenched with methanol and purified by RP-HPLC. MS: 360 M+H.

[0104] A variety of Formula I compounds where R_2 is a unsubstituted or substituted uracil can be prepared as shown by Examples 11-17.



EXAMPLE 11

6-(4-ethoxy-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)pyrimidine-2,4(1H,3H)-dione

[0105] 4-ethoxy-6-ethyl-7H-pyrrolo[2,3-d]pyrimidine-2-thiol (0.050 g, 0.220 mmol) was dissolved in acetic acid (0.750 mL) followed by addition 6-chlorouracil (0.033 g, 0.220 mmol). The reaction was heated to 100°C for 0.5 h. The reaction was allowed to cool followed by precipitation with water. The solid was collected and dried on a filter and used for the next step without further purification.

EXAMPLE 12

6-(5-chloro-4-ethoxy-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)pyrimidine-2,4(1H,3H)-dione (compound 700347).

[0106] 6-(4-ethoxy-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)pyrimidine-2,4(1H,3H)-dione (Example 11) 0.045 g, 0.134 mmol) was dissolved in acetic acid followed by addition of N-chlorosuccinimide (0.018 g, 134 mmol). The reaction was allowed to proceed at room temperature for 2 h. Water was added to precipitate the product. The filtrate was collected and dissolved in methanol and this solution was purified by RP-HPLC yielding the desired product. MS: 368 (M+H).

EXAMPLE 13

6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)pyrimidine-2,4(1H,3H)-dione

[0107] 6-chlorouracil (3 g, 20.47 mmol) and lithium bromide monohydrate (2.147 g, 20.47 mmol) was dissolved in NMP (70 mL) followed by addition of sodium hydride (0.8 g, 20.5 mmol). This mixture was allowed to stir at room temperature for 30 minutes followed by addition of SEM-Cl (3.61 mL, 20.47 mmol). The reaction proceeded for 3 h after which it was poured into a separatory funnel charged with ethyl acetate and 10% sodium carbonate solution. The organic layer was washed 3 times with brine, dried with sodium sulfate and the

solvent was removed by rotary evaporator. The product was sufficiently pure to use for the next step.

EXAMPLE 14

Ethyl 2-(4-chloro-2,6-dioxo-3-((2-(trimethylsilyl)ethoxy)methyl)-2,3-dihydropyrimidin-1(6H)-yl)acetate

[0108] 6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)pyrimidine-2,4(1H,3H)-dione (Example 13) (1 g, 3.61 mmol), NMP (12 mL) and cesium carbonate (2.4 g, 7.3 mmol) were added to a 50 mL round bottom flask followed by addition of ethyl chloroacetate (0.385 mL, 3.61 mmol). The reaction was allowed to proceed for 6 h after which it was poured into a separatory funnel charged with ethyl acetate and brine. The organic layer was washed 3x with brine and dried with sodium sulfate. The solvent was removed by rotary evaporator and the crude product was purified by flash chromatography.

EXAMPLE 15

Ethyl 2-(4-chloro-2,6-dioxo-2,3-dihydropyrimidin-1(6H)-yl)acetate

[0109] Ethyl 2-(4-chloro-2,6-dioxo-3-((2-(trimethylsilyl)ethoxy)methyl)-2,3-dihydropyrimidin-1(6H)-yl)acetate (Example 14) (1 g, 2.8 mmol) was dissolved in neat TFA. The reaction was allowed to proceed for 2 h after which the solvent was removed and the solids dissolved in ethyl ether. The solution was allowed to stand overnight and the desired compound crystallized. This compound was sufficiently pure to couple to the pyrrolopyrimidine.

EXAMPLE 16

Ethyl 2-(4-(6-ethyl-4-(3-hydroxyazetidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)-2,6-dioxo-2,3-dihydropyrimidin-1(6H)-yl)acetate

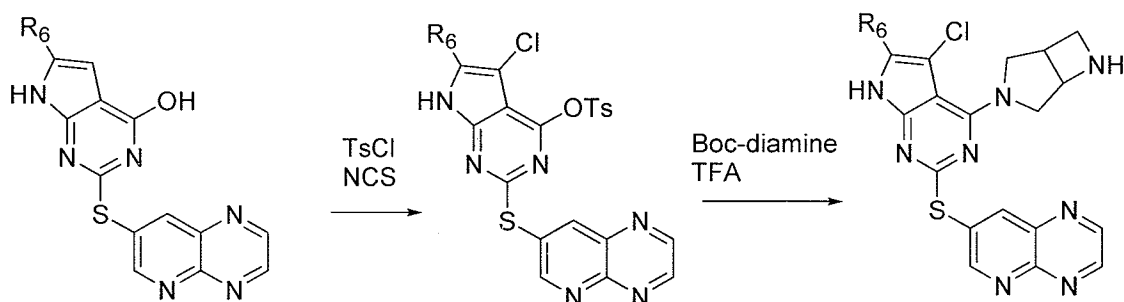
[0110] A 10 mL microwave reaction vessel was charged with ethyl 2-(4-chloro-2,6-dioxo-2,3-dihydropyrimidin-1(6H)-yl)acetate (Example 15) (9.3 mg, 0.040 mmol), 1-(6-ethyl-2-mercapto-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-ol (0.010 g, 0.040 mmol) and acetic acid (1 mL). The reaction was heated to 100°C for 0.5 h followed by addition of water to precipitate the product followed by filtration. The product was dried on a filter overnight and was used without further purification.

EXAMPLE 17

Ethyl 2-(4-(5-bromo-6-ethyl-4-(3-hydroxyazetidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)-2,6-dioxo-2,3-dihydropyrimidin-1(6H)-yl)acetate (compound 700386).

[0111] Ethyl 2-(4-(6-ethyl-4-(3-hydroxyazetidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)-2,6-dioxo-2,3-dihydropyrimidin-1(6H)-yl)acetate (Example 16) 0.02 g, 0.045 mmol) was dissolved in THF (0.150 mL) and cooled to -78°C followed by addition of N-bromosuccinimide (8 mg, 0.045 mmol). The reaction was complete within 5 min. The THF was removed by reduced pressure and the reaction was dissolved in methanol and purified by RP-HPLC. MS: 526 M+H.

[0112] A wide variety of Formula I compounds where R⁴ is a disubstituted N can be prepared from 2-arylthio-7H-pyrrolo[2,3-d]pyrimidines as shown by Examples 18-21.



EXAMPLE 18

6-ethyl-2-(pyrido[3,2-b]pyrazin-7-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yl 4-methylbenzenesulfonate

[0113] 6-ethyl-2-(pyrido[3,2-b]pyrazin-7-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-ol (1 g, 3.08 mmol) was dissolved in NMP followed by addition of sodium hydride (0.142 g, 3.7 mmol) and p-toluenesulfonyl chloride (0.705 g, 3.7 mmol). The mixture was allowed to react for 1 h after which the crude reaction was poured into water (200 mL) to induce precipitation. The precipitate was collected by filtration and dried using a vacuum oven overnight. The product was sufficiently pure to use for the next step.

EXAMPLE 19

5-chloro-6-ethyl-2-(pyrido[3,2-b]pyrazin-7-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yl 4-methylbenzenesulfonate

[0114] 6-ethyl-2-(pyrido[3,2-b]pyrazin-7-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yl 4-methylbenzenesulfonate (Example 18) (0.2 g, 0.418 mmol) was dissolved in

dichloromethane (2 mL) followed by addition of N-chlorosuccinimide (0.056 g, 0.418 mmol). The reaction was sealed and heated to 60°C for 0.5 h. The product was purified by flash chromatography on a silica column 60:40 ethyl acetate/hexane. MS: 513 m+H.

EXAMPLE 20

Tert-butyl 3-(5-chloro-6-ethyl-2-(pyrido[3,2-b]pyrazin-7-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-3,6-diazabicyclo[3.2.0]heptane-6-carboxylate

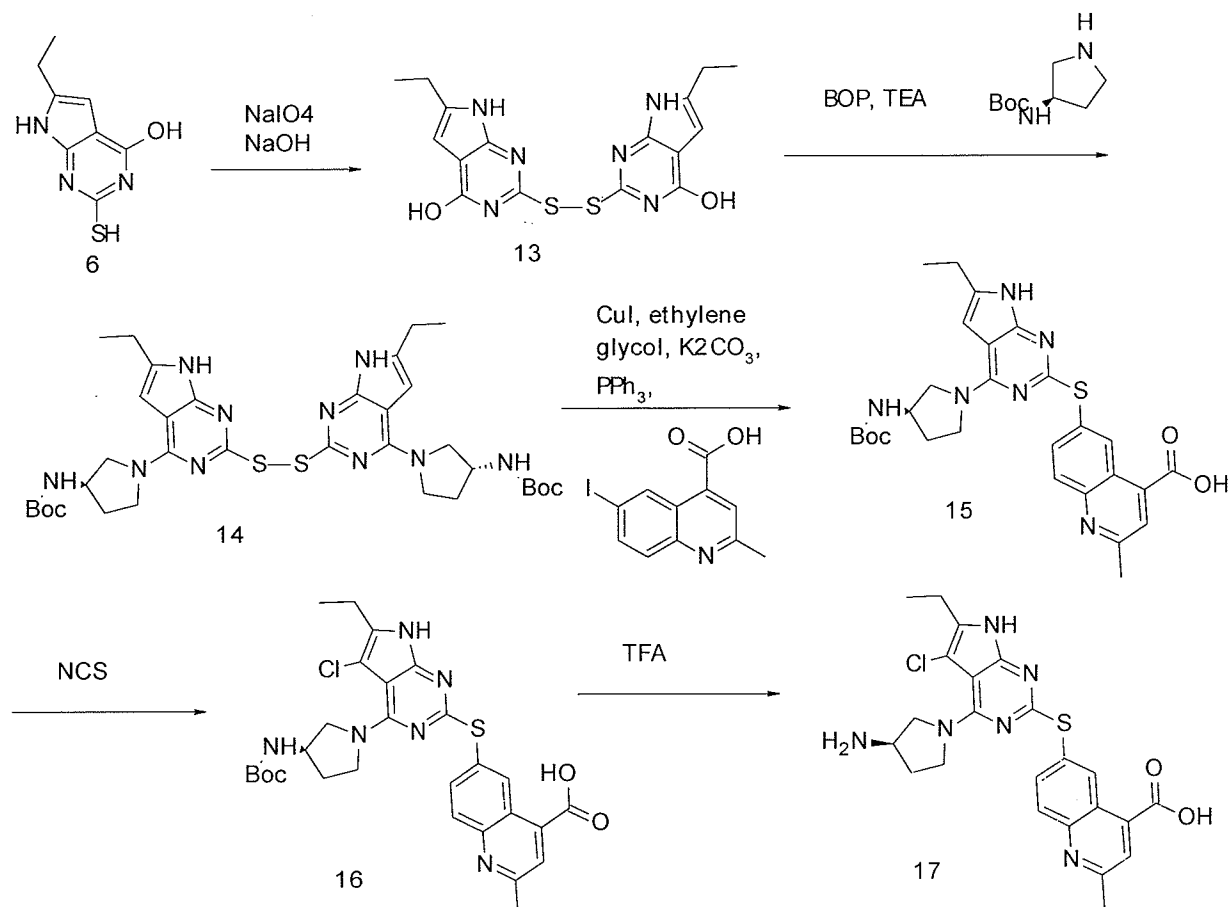
[0115] To a 10 mL microwave reaction vessel compound 5-chloro-6-ethyl-2-(pyrido[3,2-b]pyrazin-7-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yl 4-methylbenzenesulfonate (Example 19) (0.02 g, 0.039 mmol) and tert-butyl 3,6-diazabicyclo[3.2.0]heptane-6-carboxylate (7.7 mg, 0.039 mmol) was dissolved in ethanol (0.1 mL). The reaction was sealed and heated to 100°C for 0.5 h after which the solvent was removed and the crude was used for the next step without further purification

EXAMPLE 21

7-(4-(3,6-diazabicyclo[3.2.0]heptan-3-yl)-5-chloro-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)pyrido[3,2-b]pyrazine (compound 700548).

[0116] Crude tert-butyl 3-(5-chloro-6-ethyl-2-(pyrido[3,2-b]pyrazin-7-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-3,6-diazabicyclo[3.2.0]heptane-6-carboxylate (Example 20) was dissolved in trifluoroacetic acid (0.1 mL) and allowed to react for 30 minutes after which the solvent was removed. The crude was dissolved in methanol and injected directly on the preparative RP-HPLC for purification which yielded the desired product. MS: 540 M+H.

[0117] A broad range of Formula I compounds can be prepared from various 4-pyrrolidines-2-thio-7H-pyrrolo[2,3-d]pyrimidines that can be generated from disulfides as shown in Examples 22-25.



EXAMPLE 22

2,2'-disulfanediyldis(6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ol)

[0118] 6-ethyl-2-mercapto-7H-pyrrolo[2,3-d]pyrimidin-4-ol (Example 2) (5 g, 25.6 mmol) was suspended in water (250 mL) followed by addition of sodium hydroxide (2 M, 26 mL, 51 mmol). The mixture was allowed to stir at room temperature until all the pyrrolopyrimidine dissolved. Sodium periodate (5.48 g, 25.6 mmol) was dissolved in water (25 mL) and this solution was added to the reaction and allowed to stir for 5 h at room temperature. The reaction was neutralized with 1 M HCl and the resulting solid was collected and dried on a sinter glass funnel. The reaction was quantitative and sufficiently pure to use for the next step.

EXAMPLE 23

tert-butyl (3R,3'R)-1,1'-(2,2'-disulfanediy)bis(6-ethyl-7H-pyrrolo[2,3-d]pyrimidine-4,2-diyl))bis(pyrrolidine-3,1-diyl)dicarbamate.

[0119] 2,2'-disulfanediy)bis(6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ol (0.5 g, 1.287 mmol) was suspended in DMF (5 mL) and cooled to 0° C followed by the addition of BOP reagent (1.42 g, 3.22 mmol) and triethylamine (7.2 mL, 5.1 mmol). The reaction was allowed to proceed to the activated ether after which (R)-tert-butyl pyrrolidin-3-ylcarbamate (0.48 g, 2.6 mmol) was added. The reaction was allowed to proceed for 12 h at room temperature after which the crude was added dropwise to water (200 mL). The precipitate was collected by filtration and allowed to dry. The product was used for the next step without further purification.

EXAMPLE 24

(R)-6-(4-(3-(tert-butoxycarbonylamino)pyrrolidin-1-yl)-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)-2-methylquinoline-4-carboxylic acid

[0120] tert-butyl (3R,3'R)-1,1'-(2,2'-disulfanediy)bis(6-ethyl-7H-pyrrolo[2,3-d]pyrimidine-4,2-diyl))bis(pyrrolidine-3,1-diyl)dicarbamate (Example 23) (0.1 g, 0.138 mmol), 6-iodo-2-methylquinoline-4-carboxylic acid (0.086 g, 0.28 mmol), triphenylphosphine (0.036 g, 0.138 mmol), and potassium carbonate (0.038 g, 0.276 mmol) were dissolved in NMP (0.5 mL). A small test tube was charged with copper iodide (2.6 mg, 0.014 mmol) NMP (0.1 mL) and N,N'-dimethylcyclohexane-1,2-diamine (0.004 g, 0.028 mmol). The copper solution was allowed to react for 10 min and added to the reaction mixture followed by flushing the reaction with nitrogen, sealing the reaction and heating to 130 °C for 1h. Upon completion of the coupling the reaction was diluted with methanol (1 mL) and injected directly on the HPLC for purification. MS 549 (M+H+).

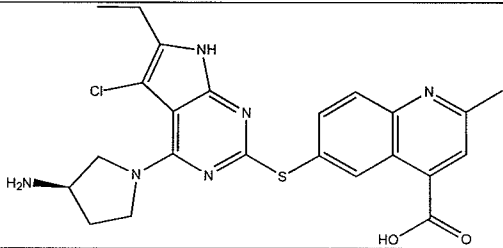
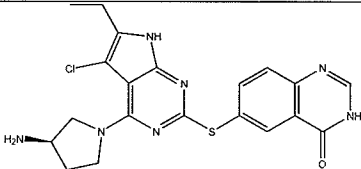
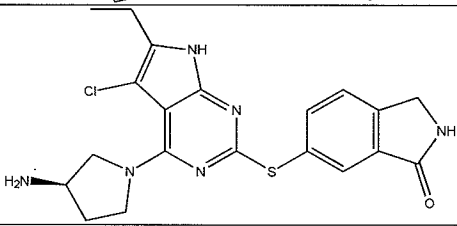
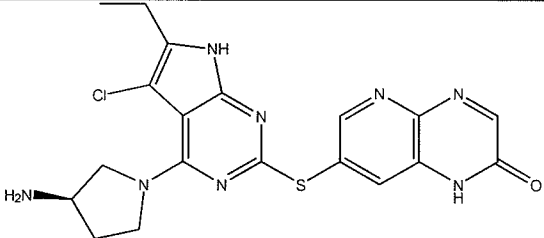
EXAMPLE 25

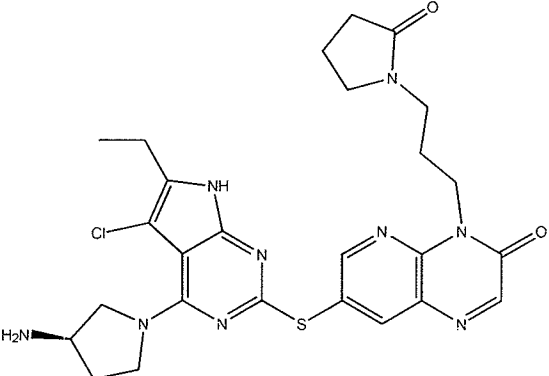
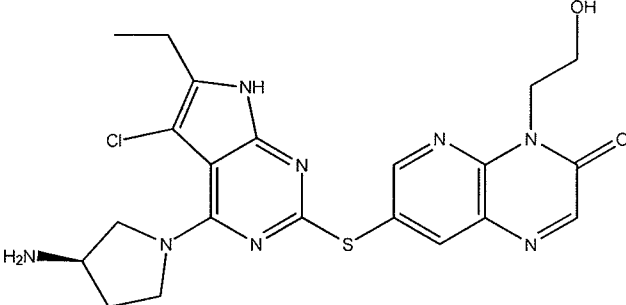
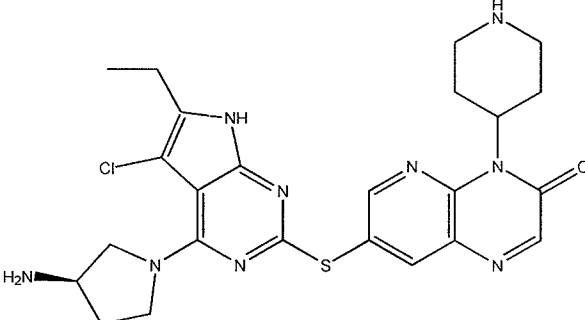
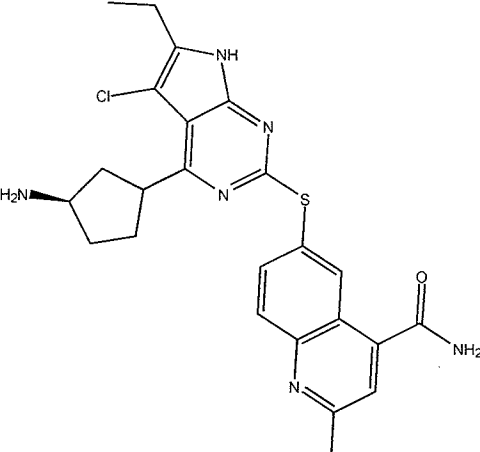
(R)-6-(4-(3-aminopyrrolidin-1-yl)-5-chloro-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)-2-methylquinoline-4-carboxylic acid (compound 700708)

(R)-6-(4-(3-(tert-butoxycarbonylamino)pyrrolidin-1-yl)-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)-2-methylquinoline-4-carboxylic acid (Example 24) (0.036 g, 0.066 mmol) was suspended in dichloromethane (1 mL). N-chlorosuccinimide (8.8 mg, 0.066

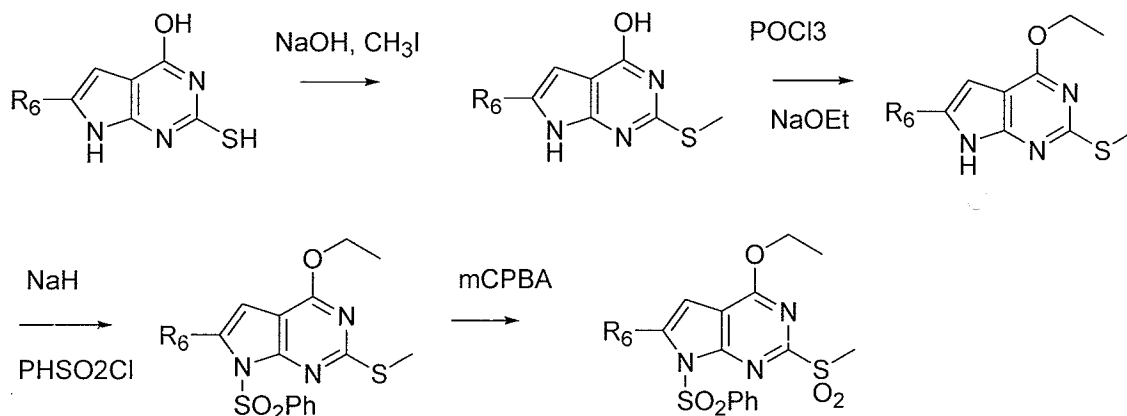
mmol) was added to the suspension and the reaction was sealed and heated to 60 °C for 30 minutes. The reaction was allowed to cool to room temperature followed by the addition of trifluoroacetic acid (1 mL). Boc removal proceeded smoothly and after 15 minutes the solvent was removed and the crude product was dissolved in methanol and purified by reverse phase HPLC. MS 483 (M+H⁺).

[0121] The following compounds were made following a similar procedure as Examples 22-25.

Rx ID	product	LC-MS
700708		
700710		
700711		
700712		

700797		
700798		
700799		
700862		

[0122] The intermediate from Example 2 can be converted into a 2-(methylsulfonyl)-pyrrolo[2,3-d]pyrimidine intermediate useful in preparing Formula I compounds where L = N as shown in Examples 26-30.



EXAMPLE 26

6-Ethyl-2-(methylthio)-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one

[0123] To a suspension of 6-ethyl-2-sulfanyl-3,4a,7,7a-tetrahydro-4H-pyrrolo[2,3-d]pyrimidin-4-one (tautomeric form of Example 2) (2.00 g, 10.24 mmol) and NaOH (3.85 g, 96.3 mmol) in EtOH (50 mL) was added CH₃I (0.64 mL, 10.3 mmol) dropwise. The resulting mixture was vigorously stirred for one hour at room temperature. Solvents were removed under the reduced pressure. The residue was dissolved the minimum amount of water and then acidified with 6 M HCl to PH about 3. The precipitate was collected by filtration, washed with water and dried to give 6-Ethyl-2-(methylthio)-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one 1.80 g (84%) as a white powder. MS (ESI) m/z 210 (M + H)⁺.

EXAMPLE 27

4-Chloro-6-ethyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine

[0124] Phosphorous oxychloride (17.6 mL, 192.3 mmol) was carefully added to a mixture of 6-ethyl-2-(methylthio)-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one (Example 26) (4.75 g, 22.7 mmol) and N,N-dimethylaniline (1.5 mL, 11.8 mmol) at room temperature. The reaction mixture was then heated to 95°C for 12 h, cooled to room temperature. The excess of POCl₃ was removed under the reduced pressure. Ice water (50 g) was added and the precipitate was collected by filtration, dried to give a solid 4-chloro-6-ethyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine 3.87 g (75%). MS (ESI) m/z 228 (M + H)⁺.

EXAMPLE 28

4-Ethoxy-6-ethyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine

[0125] A mixture of 4-chloro-6-ethyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine (Example 27) (1.01 g, 4.44 mmol), 21% wt. sodium ethoxide (10 mL, 25.2 mmol) was heated in a microwave oven at 150°C for one hour. Water (120 mL) was added to the reaction mixture. The precipitate was collected and dried to give 4-ethoxy-6-ethyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine 1.04 g (99%) as a grey powder. MS (ESI) m/z 238 (M + H)⁺.

EXAMPLE 29

4-Ethoxy-6-ethyl-2-(methylthio)-7-(phenylsulfonyl)-7H-pyrrolo[2,3-d]pyrimidine

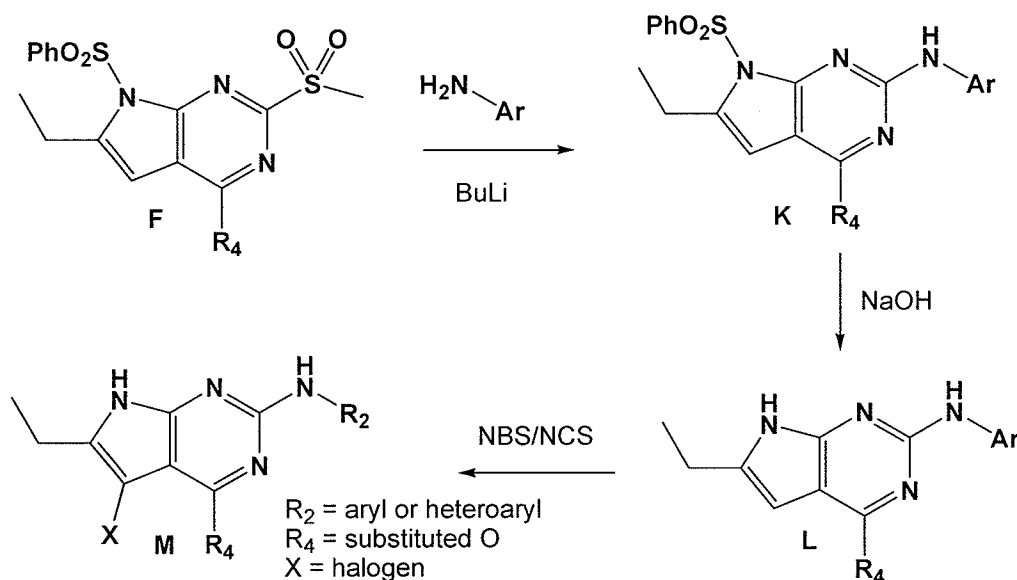
[0126] NaH (60% in mineral oil, 186.4 mg, 4.66 mmol) was added to 10 mL of DMF cooled to 0°C, followed by addition of 4-ethoxy-6-ethyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine (Example 28) (1.05 g, 4.42 mmol) in DMF (10 mL) over 5 minutes. The stirring was continued for 15 minutes at 0°C, then benzenesulfonyl chloride (0.4 mL, 3.11 mmol) was added dropwise. After addition, the reaction mixture was warmed up to room temperature and stirred for one hour. Water (150 mL) was added. The precipitate was collected by filtration and dried to give 4-ethoxy-6-ethyl-2-(methylthio)-7-(phenylsulfonyl)-7H-pyrrolo[2,3-d]pyrimidine 1.35 g (81%) as a white solid. MS (ESI) m/z 378 (M + H)⁺.

EXAMPLE 30

4-Ethoxy-6-ethyl-2-(methylsulfonyl)-7-(phenylsulfonyl)-7H-pyrrolo[2,3-d]pyrimidine

[0127] m-Chloroperoxybenzoic acid (MCPBA, 1.37 g, 77%, 6.11 mmol) was added to a stirring solution of 4-ethoxy-6-ethyl-2-(methylthio)-7-(phenylsulfonyl)-7H-pyrrolo[2,3-d]pyrimidine (Example 29) (0.884 g, 2.35 mmol) in DMF (33 mL) at room temperature. The stirring was continued for 17 h. Water (80 mL) was added. The precipitate was filtered to give 0.81 g of white solid product which was contaminated with MCPBA. Ether (1 mL) was added to the white solid and the suspension was filtered to give 4-ethoxy-6-ethyl-2-(methylsulfonyl)-7-(phenylsulfonyl)-7H-pyrrolo[2,3-d]pyrimidine 0.64 g (67%) as a white powder. MS (ESI) m/z 410 (M + H)⁺.

[0128] The intermediate prepared in Example 30 may be converted into a variety of Formula I compounds where L = N and R⁴ is a substituted O as shown by Examples 31-33.



EXAMPLE 31

Preparation of 4-Ethoxy-6-ethyl-7-(phenylsulfonyl)-N-(pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (Compound K)

[0129] n-BuLi (1.6 M in hexanes, 0.62 mL, 1 mmol) was added dropwise to a cooled stirring solution of an amine, 3-aminopyridine ($\text{H}_2\text{N-Ar}$) (1 mmol) in THF (3 to 5 mL, depending on solubility) at -78°C . The stirring was continued for 20 minutes at -78°C , then the resulting solution was quickly transferred into a stirring solution of compound F (Example 30) (102 mg, 0.25 mmol) in THF (2 mL) at room temperature. After 5 minutes stirring, water (25 mL) was added. The mixture was extracted with EtOAc (3 X 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. Flash chromatography of the residue over silica gel (eluent: 20% EtOAc/hexanes) to give 4-Ethoxy-6-ethyl-7-(phenylsulfonyl)-N-(pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (compound K).

EXAMPLE 32

Preparation of 4-Ethoxy-6-ethyl-N-(pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (Compound L)

[0130] 4-Ethoxy-6-ethyl-7-(phenylsulfonyl)-N-(pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (Compound K) (0.088 mmol) was added to a stirring solution of NaOH (0.3 g, 7.5 mmol) in THF (2 mL) and MeOH (1 mL). The stirring was continued for 15 minutes. LC-MS indicated the reaction was completed. TFA (3 mL) was added to the

reaction mixture. The solvents were removed under the reduced pressure. The resulting residue (L) was used directly for the next step.

EXAMPLE 33

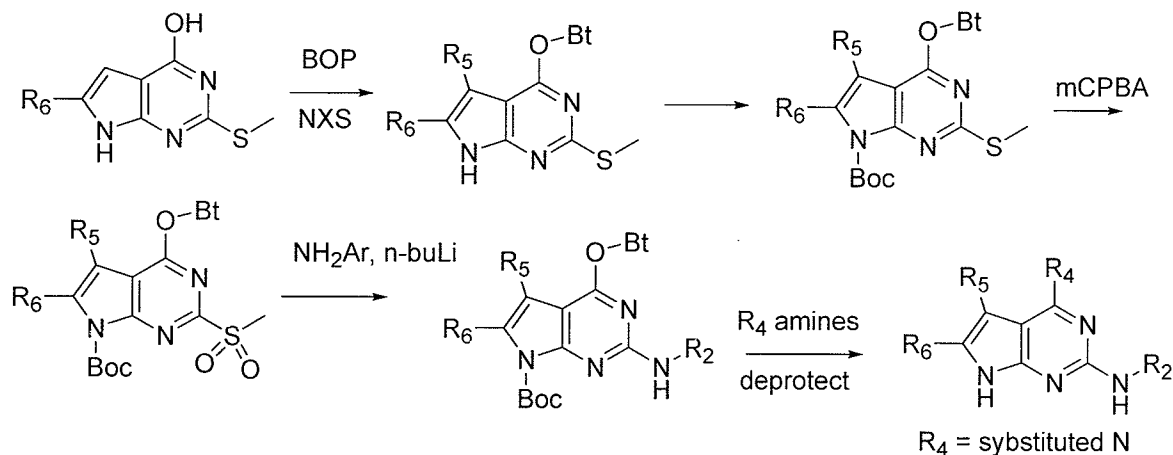
Preparation of 5-bromo-4-ethoxy-6-ethyl-N-(pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (Compound M)

[0131] N-Bromosuccinimide (NBS) or N-chlorosuccinimide (NCS) (0.088 mmol) was added to a stirring solution of 4-Ethoxy-6-ethyl-N-(pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (compound L) (0.088 mmol) in THF (3 mL) at room temperature. In the case of NBS, MeOH (5 mL) was added to the reaction mixture within 5 minutes after addition. For NCS, LC-MS monitoring the reaction, and the reaction usually took several h to complete, occasionally heating needed. After removal of all solvents, the residue was dissolved in DMSO (2 mL) which was separated by prep-HPLC (CH₃CN/H₂O in 0.1% TFA) to give compound M in above scheme. give 5-bromo-4-ethoxy-6-ethyl-N-(pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine.

[0132] Additional analogs prepared by the scheme exemplified by Examples 31-33 include:

- N-(5-bromo-4-ethoxy-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-yl)quinolin-3-amine
- N-(5-bromo-4-ethoxy-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-yl)-1-isopropyl-1H-pyrazolo[3,4-b]pyridin-5-amine
- N-(5-chloro-4-ethoxy-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-yl)-1-isopropyl-1H-pyrazolo[3,4-b]pyridin-5-amine
- 5-bromo-4-ethoxy-6-ethyl-N-(pyrimidin-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine
- 5-chloro-4-ethoxy-6-ethyl-N-(pyrimidin-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine

[0133] Compounds of Formula I where L = N and R⁴ is a substituted N may be prepared as shown by Examples 34-41 using the methyl sulfide intermediate described in Example 26.



EXAMPLE 34

1-(6-Ethyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)-1H-benzo[d][1,2,3]triazole

[0134] Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium

hexafluorophosphate (BOP, 9.52 g, 21.5 mmol) was added slowly to a stirring solution of 6-ethyl-2-(methylthio)-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one (Example 26) (3.6 g, 17.2 mmol), Et₃N (3.0 mL, 21.5 mmol) in NMP (100 mL) at 0°C. The stirring was continued for 30 minutes at 0°C, and then 30 minutes at room temperature. HOBT (2.33 g, 17.2 mmol) and Et₃N (2.4 mL, 17.2 mmol) was added. The mixture was heated to 40°C for 12 h (LC-MS monitoring reaction). Water (300 mL) was added to the reaction mixture. The precipitate was collected by filtration and dried to give 4.4 g (78%) of 1-(6-Ethyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)-1H-benzo[d][1,2,3]triazole. MS (ESI) m/z 327 (M + H)⁺.

EXAMPLE 35

1-(5-Bromo-6-ethyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)-1H-benzo[d][1,2,3]triazole

[0135] N-Bromosuccinimide (0.530 g, 2.98 mmol) was added portion-wise to a stirring solution of 1-(6-ethyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)-1H-benzo[d][1,2,3] triazole (0.97 g, 2.98 mmol) in THF (50 mL). The stirring was continued for 5 minutes after addition, and then half of the THF was removed under the reduced pressure. Water (50 mL) was added. The precipitate was filtered and dried to give 0.88 g (73%) of the grey solid 1-(5-bromo-6-ethyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)-1H-benzo[d][1,2,3]triazole. MS (ESI) m/z 407 (M + H)⁺.

EXAMPLE 36

Tert-Butyl 4-(1H-benzo[d][1,2,3]triazol-1-yloxy)-5-bromo-6-ethyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate

[0136] Di-tert-butyl dicarbonate (327 mg, 1.50 mmol) was added to a stirring solution of 1-(5-bromo-6-ethyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)-1H-benzo[d][1,2,3]triazole (368 mg, 0.910 mmol), Et₃N (0.28 mL, 2.0 mmol) and 4-dimethylaminopyridine (25 mg, 0.2 mmol) in THF (25 mL) at room temperature. The stirring was continued for one hour. LC-MS indicated that the reaction was completed. Water (50 mL) was added. The mixture was extracted with EtOAc (3 X 80 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. Flash chromatography of the residue over silica gel (eluent: 20% EtOAc/hexane) to give 344 mg (75%) of tert-butyl 4-(1H-benzo[d][1,2,3]triazol-1-yloxy)-5-bromo-6-ethyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate. MS (ESI) m/z 507 (M + H)⁺.

EXAMPLE 37

Tert-Butyl 4-(1H-benzo[d][1,2,3]triazol-1-yloxy)-5-bromo-6-ethyl-2-(methylsulfonyl)-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate)

[0137] m-Chloroperoxybenzoic acid (MCPBA, 487 mg, 77%, 2.17 mmol) was added to a stirring solution of tert-butyl 4-(1H-benzo[d][1,2,3]triazol-1-yloxy)-5-bromo-6-ethyl-2-(methylthio)-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate (0.423 g, 0.836 mmol) in DMF (12 mL) at room temperature. The stirring was continued for 17 h. Water (50 mL) was added. The mixture was extracted with EtOAc (3 X 80 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. Flash chromatography of the residue over silica gel (eluent: 30% EtOAc/hexane) to give 330 mg (73%) of Tert-butyl 4-(1H-benzo[d][1,2,3]triazol-1-yloxy)-5-bromo-6-ethyl-2-(methylsulfonyl)-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate. MS (ESI) m/z 539 (M + H)⁺.

EXAMPLE 38

Tert-butyl 4-(1H-benzo[d][1,2,3]triazol-1-yloxy)-5-bromo-6-ethyl-2-(3-isopropyl-3H-[1,2,3]triazolo[4,5-b]pyridin-6-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate.

[0138] n-BuLi (1.6 M in hexanes, 0.35 mL, 0.56 mmol) was added dropwise to a cooled stirring solution of an amine, 3-isopropyl-3H-[1,2,3]triazolo[4,5-b]pyridin-6-amine

(99 mg, 0.56 mmol) in THF (2 mL) at -78°C. The stirring was continued for 20 minutes at -78°C, then the resulting solution was quickly transferred into a stirring solution of J (100 mg, 0.186 mmol) in THF (1 mL) at room temperature. After 5 minutes stirring, water (20 mL) was added. The mixture was extracted with EtOAc (3 X 30 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. Flash chromatography of the residue over silica gel (eluent: 20% EtOAc/hexanes) to give the desired product 47 mg (40%). MS (ESI) m/z 634 (M + H)⁺.

EXAMPLE 39

1-(5-Bromo-6-ethyl-2-(3-isopropyl-3H-[1,2,3]triazolo[4,5-b]pyridin-6-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-ol.

[0139] Azetidin-3-ol hydrochloride (6.5 mg, 0.06 mmol) was added to a stirring solution of Et₃N (20 µL) and tert-butyl 4-(1H-benzo[d][1,2,3]triazol-1-yloxy)-5-bromo-6-ethyl-2-(3-isopropyl-3H-[1,2,3]triazolo[4,5-b]pyridin-6-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate (Example 38) (19 mg, 0.03 mmol) in NMP (0.7 mL). The stirring was continued for 6 h. LC-MS indicated the reaction was completed. DMSO (0.5 mL) was added to the mixture. The solution was subjected to prep-HPLC (CH₃CH₂-H₂O, in 0.1% TFA) to give the desired product. MS (ESI) m/z 472 (M + H)⁺.

EXAMPLE 40

tert-butyl 1-(5-bromo-6-ethyl-2-(3-isopropyl-3H-[1,2,3]triazolo[4,5-b]pyridin-6-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-ylcarbamate.

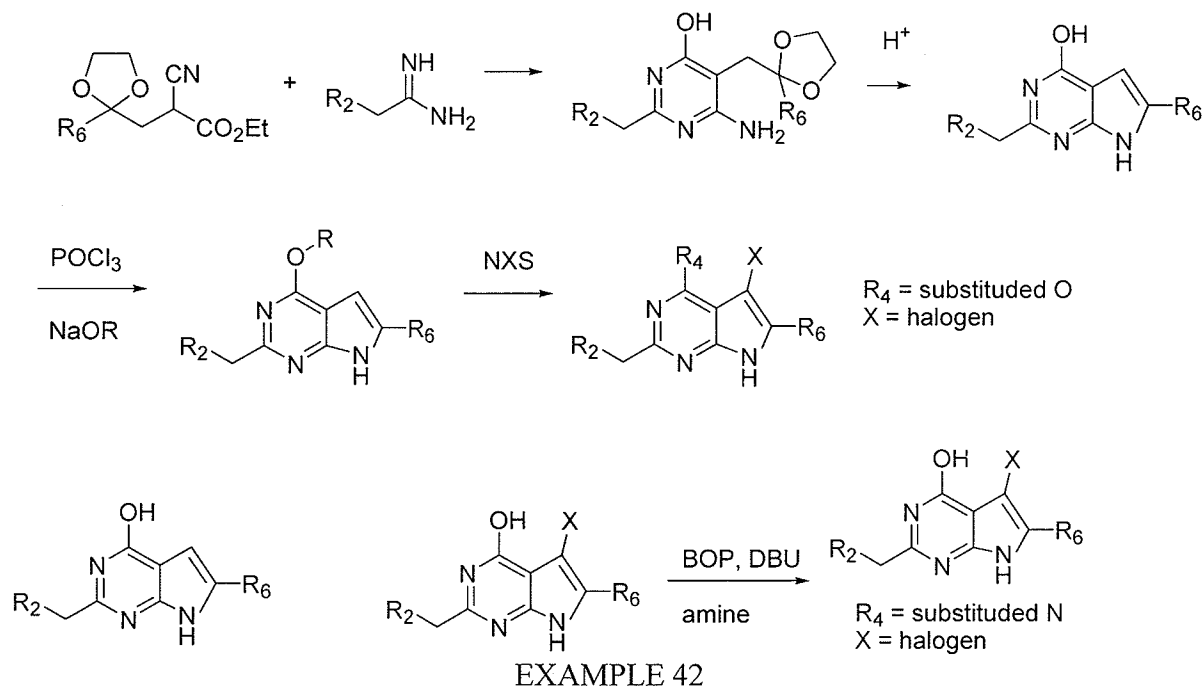
[0140] tert-butyl azetidin-3-ylcarbamate (8.3 mg, 0.048 mmol) was added to a stirring solution of Et₃N (20 µL) tert-butyl 4-(1H-benzo[d][1,2,3]triazol-1-yloxy)-5-bromo-6-ethyl-2-(3-isopropyl-3H-[1,2,3]triazolo[4,5-b]pyridin-6-ylamino)-7H-pyrrolo[2,3-d]pyrimidine-7-carboxylate (Example 39) (15 mg, 0.024 mmol) in NMP (0.7 mL). The stirring was continued for 8 h. LC-MS indicated the reaction was completed. DMSO (0.5 mL) was added to the mixture. The solution was subjected to prep-HPLC (CH₃CH₂-H₂O, in 0.1% TFA) to give the desired product. MS (ESI) m/z 571 (M + H)⁺.

EXAMPLE 41

N-(4-(3-aminoazetidin-1-yl)-5-bromo-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-yl)-3-isopropyl-3H-[1,2,3]triazolo[4,5-b]pyridin-6-amine.

[0141] A solution of tert-butyl 1-(5-bromo-6-ethyl-2-(3-isopropyl-3H-[1,2,3]triazolo[4,5-b]pyridin-6-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-ylcarbamate (Example 40) (2 mg) in TFA (0.5 mL) was stirring for 30 minutes. LC-MS indicated the reaction was completed. Removal of solvents under the reduced pressure gave the pure desired product. MS (ESI) m/z 471 ($M + H$)⁺.

[0142] Compounds of Formula I where L = C and R⁴ is a substituted N or a substituted O may be prepared as shown by Examples 42-49.



6-amino-5-((2-ethyl-1,3-dioxolan-2-yl)methyl)-2-(pyridin-3-ylmethyl)pyrimidin-4-ol

[0143] Ethyl cyanoacetate (35 mL, 331 mmol) was dissolved in toluene (1.5 L) and DBU (50 mL, 331 mmol) was added via dropping funnel. The reaction was allowed to stir for 30 minutes. The pot was placed in an ice bath and allowed to cool to 0°C followed by dropwise addition of 1-bromo-2-butanone (50 g, 331 mmol). This reaction was slightly exothermic so it was monitored and the temperature was not allowed to rise over 10°C. Once addition was complete the reaction turned a brown color. It was allowed slowly warm to room temperature and to react overnight. The next morning the reaction was poured into a separatory funnel and washed 2x with 1 M HCl and 1x with brine. The organic layer was dried with sodium sulfate and filtered. The toluene was removed by rotary evaporator to yield

50 grams of a dark brown liquid. The product was pure as determined by NMR and was carried on to the next step.

[0144] Ethyl 2-cyano-4-oxohexanoate (50 g, 273 mmol) was dissolved in benzene (550 mL). To this solution was added ethylene glycol (22.8 mL, 409 mmol) and p-toluenesulfonic acid monohydrate (1 g, 5.46 mmol). The reaction was equipped with a Dean-Stark trap, a heating mantle and a reflux condenser and the reaction was heated to reflux until the appropriate amount of water was removed from the reaction, anywhere from 2-12 h. The reaction was cooled and poured into a separatory funnel and washed 2x with 10% sodium carbonate and 1x with brine. The organic layer was dried with sodium sulfate, filtered and the solvent removed by rotary evaporator to yield a dark oil. NMR indicated this product was about >90% pure therefore we used it for the next step without further purification.

[0145] 2-(pyridin-3-yl)-acetimidamide (1.4 g, 10 mmol) was suspended in dry ethanol (30 mL) and sodium ethoxide (21% solution) (50 mL, 13 mmol) was added. To this reaction was added ethyl 2-cyano-3-(2-ethyl-1,3-dioxolan-2-yl)propanoate (Example 56) (0.3 g, 10 mmol). The reaction was equipped with a mechanical stirrer, a heating mantle and a reflux condenser and heated to reflux for 6 h during which a precipitate was observed. The next morning the solvent was removed and water (30 mL) was added to the crude product followed by addition of 10% citric acid to pH 7. The solid was collected and the wet cake was washed with cold ethanol to remove most of the brown discoloration. The cake was dried in a vacuum oven overnight to yield the desired amino pyrimidine. The product was used without further purification.

EXAMPLE 43

6-ethyl-2-(pyridin-3-ylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ol

[0146] 6-amino-5-((2-ethyl-1,3-dioxolan-2-yl)methyl)-2-(pyridin-3-ylmethyl)pyrimidin-4-ol (Example 60) (2 g) was added to THF (10 mL) and to this suspension was added 1 N HCl in water (10 mL). The pyrimidine slowly dissolves in this solution over a 1 h period and a new precipitate forms. The reaction was allowed to proceed overnight and the next day the precipitate was collect via filtration. The filter cake was washed with water and dried in a vacuum oven overnight.

EXAMPLE 44

4-chloro-6-ethyl-2-(pyridin-3-ylmethyl)-7H-pyrrolo[2,3-d]pyrimidine

[0147] 6-ethyl-2-(pyridin-3-ylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ol (Example 61) (500 mg) was dissolved in phosphorous oxychloride (5 mL) and 0.1 mL Hunigs base, and heated to reflux for 3 h. Then the phosphorous oxychloride was removed by rotary evaporator and the remaining syrup was carefully quenched with 100 mL of chipped ice. The precipitate was collected and washed with water and dried in a vacuum oven overnight.

EXAMPLE 45

6-ethyl-2-(pyridin-3-ylmethyl)-4-(pyridin-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidine

[0148] Sodium hydride (20 mg) was added into 20 mg pyridin-3-ol in 2 mL NMP and stirred for 5 min, then 4-chloro-6-ethyl-2-(pyridin-3-ylmethyl)-7H-pyrrolo[2,3-d]pyrimidine (Example 44) (10 mg) was added into above solution, the mixture was heated to 160°C for 20 min, and cooled to ambient temperature, and quenched by 0.5 mL 1 M HCl, the reaction solution was injected to reverse phase HPLC and provided the title compounds, LCMS: 332(M+H).

EXAMPLE 46

5-chloro-6-ethyl-2-(pyridin-3-ylmethyl)-4-(pyridin-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidine

[0149] 6-ethyl-2-(pyridin-3-ylmethyl)-4-(pyridin-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidine (Example 63) (5 mg) was dissolved into 1 mL NMP, then 2 mg NCS was added into the solution, the reaction was monitored by LCMS, after 6-ethyl-2-(pyridin-3-ylmethyl)-4-(pyridin-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidine disappeared, the reaction solution was injected to reverse phase HPLC and provided the title compounds, LCMS: 366(M+H).

EXAMPLE 47

5-chloro-6-ethyl-2-(pyridin-3-ylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ol

[0150] 6-ethyl-2-(pyridin-3-ylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ol (Example 43) (30 mg) was dissolved into 2 mL NMP, then 20 mg NCS was added into the solution, the reaction was monitored by LCMS, after the compounds 8 disappeared, the reaction solution was injected to reverse phase HPLC and provided the title compounds, LCMS: 289(M+H).

EXAMPLE 48

1-(6-ethyl-5-methyl-2-(pyridin-3-ylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-amine

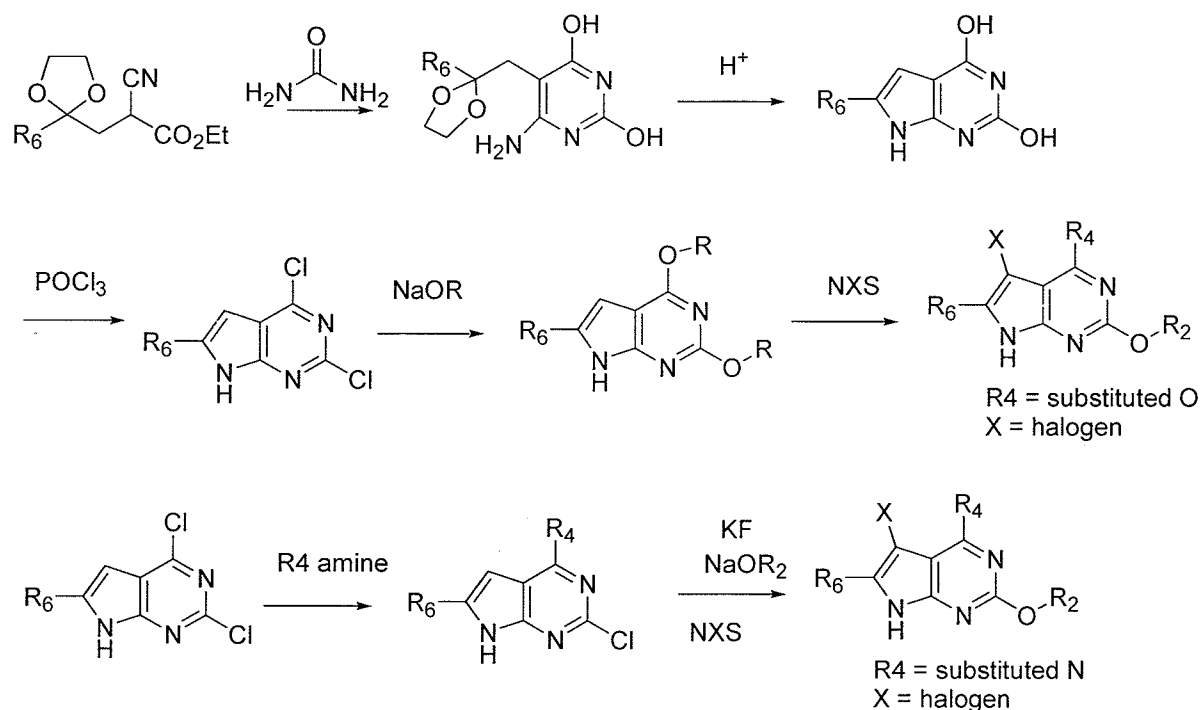
[0151] 5-chloro-6-ethyl-2-(pyridin-3-ylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ol (Example 47) (5 mg) was dissolved into 1 mL DMF, then 10 mg BOP and 20 μ L DBU was added into the solution at 0~5°C, the solution was stirred for 10 min, then *tert*-butyl azetidin-3-ylcarbamate 10 mg was added into the previous solution, the reaction solution was stirred for overnight, and then the reaction solution was injected to reverse phase HPLC and purified. The purified compounds was dried and re-dissolved into 1 mL TFA and stirred for 0.5 hour, then removed the excess TFA to give the title compound, LCMS: 343 (M+H).

EXAMPLE 49

1-(5-chloro-6-ethyl-2-(pyridin-3-ylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-ol

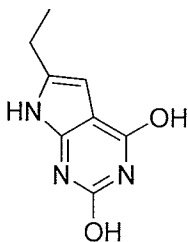
[0152] 5-chloro-6-ethyl-2-(pyridin-3-ylmethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ol (Example 48) (5 mg) was dissolved into 1 mL DMF, then 10 mg BOP and 20 μ L DBU was added into the solution at 0~5°C, the solution was stirred for 10 min, then *tert*-butyl azetidin-3-ylcarbamate 10 mg was added into the previous solution, the reaction solution was stirred for overnight, and then the reaction solution was injected to reverse phase HPLC and provided the title compounds, LCMS: 344 (M+H).

[0153] Compounds of Formula I where L = O and R⁴ is a substituted N or a substituted O may be prepared as shown by Examples 50-55.



EXAMPLE 50

6-ethyl-7H-pyrrolo[2,3-d]pyrimidine-2,4-diol



[0154] Ethyl cyanoacetate (35 mL, 331 mmol) was dissolved in toluene (1.5 L) and DBU (50 mL, 331 mmol) was added via dropping funnel. The reaction was allowed to stir for 30 minutes. The pot was placed in an ice bath and allowed to cool to 0°C followed by dropwise addition of 1-bromo-2-butanone (50 g, 331 mmol). This reaction was slightly exothermic so it was monitored and the temperature was not allowed to rise over 10°C. Once addition was complete the reaction turned a brown color. It was allowed slowly warm to room temperature and to react overnight. The next morning the reaction was poured into a separatory funnel and washed 2x with 1 M HCl and 1x with brine. The organic layer was dried with sodium sulfate and filtered. The toluene was removed by rotary evaporator to yield 50 grams of a dark brown liquid. The product was pure as determined by NMR and was carried on to the next step.

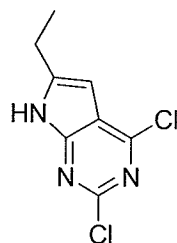
[0155] Ethyl 2-cyano-4-oxohexanoate (50 g, 273 mmol) from above was dissolved in benzene (550 mL). To this solution was added ethylene glycol (22.8 mL, 409 mmol) and p-toluenesulfonic acid monohydrate (1 g, 5.46 mmol). The reaction was equipped with a Dean-Stark trap, a heating mantle and a reflux condenser and the reaction was heated to reflux until the appropriate amount of water was removed from the reaction, anywhere from 2-12 h. The reaction was cooled and poured into a separatory funnel and washed 2x with 10% sodium carbonate and 1x with brine. The organic layer was dried with sodium sulfate, filtered and the solvent removed by rotary evaporator to yield a dark oil. NMR indicated this product was about >90% pure therefore we used it for the next step without further purification.

[0156] Urea (18.0 g, 264 mmol) was suspended in dry ethanol (400 mL) and sodium ethoxide (21% solution) (100 mL, 264 mmol) was added. To this reaction was added ethyl 2-cyano-3-(2-ethyl-1,3-dioxolan-2-yl)propanoate (60 g, 264 mmol). The reaction was equipped with a mechanical stirrer, a heating mantle and a reflux condenser and heated to reflux for 6 h during which a precipitate was observed. The next morning the solvent was removed and water (300 mL) was added to the crude product followed by addition of 10% citric acid to pH 7. The solid was collected and the wet cake was washed with cold ethanol to remove most of the brown discoloration. The cake was dried in a vacuum oven overnight to yield the desired amino pyrimidine. The product was used without further purification.

[0157] 6-amino-5-((2-ethyl-1,3-dioxolan-2-yl)methyl)pyrimidine-2,4-diol (16 g) was added to THF (50 mL) and to this suspension was added 1 M HCl in water (500 mL). The pyrimidine slowly dissolved in this solution over a 1 h period and a new precipitate formed. The reaction was allowed to proceed overnight and the next day the precipitate was collect via filtration. The filter cake was washed with water and dried in a vacuum oven overnight.

EXAMPLE 51

2,4-dichloro-6-ethyl-7H-pyrrolo[2,3-d]pyrimidine



[0158] 6-amino-5-((2-ethyl-1,3-dioxolan-2-yl)methyl)pyrimidine-2,4-diol (Example 50) (10 g) was dissolved in phosphorous oxychloride (20 mL) and 1 mL Hunigs base, and heated to reflux for 3 h. Then the phosphorous oxychloride was removed by rotary evaporator and the remaining syrup was carefully quenched with 100 mL of chipped ice. The precipitate was collected and washed with water and dried in a vacuum oven overnight.

EXAMPLE 52

6-Ethyl-2,4-bis(pyridin-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidine

[0159] 2,4-dichloro-6-ethyl-7H-pyrrolo[2,3-d]pyrimidine (Example 51) (100 mg, 0.46 mmol) was combined with potassium carbonate (80 mg, 0.5 mmol), 3-hydroxypyridine (88 mg, 0.92 mmol), NMP (5 mL). The reaction was purged with dry nitrogen and heated to 120°C by microwave for 10 min. The NMP was removed by rotary evaporator and the crude product was purified by HPLC. A white solid product was obtained (90 mg), LCMS: 334.21.

EXAMPLE 53

5-chloro-6-ethyl-2,4-bis(pyridin-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidine

[0160] Using the procedure described in Example 25, the title compound was obtained. A white solid product was obtained (20 mg), LCMS: 368.32.

EXAMPLE 54

5-chloro-6-ethyl-2,4-bis(5-fluoropyridin-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidine

[0161] Using the procedure described in Examples 52 and 53 the title compound was obtained. LCMS: 368.32.

EXAMPLE 55

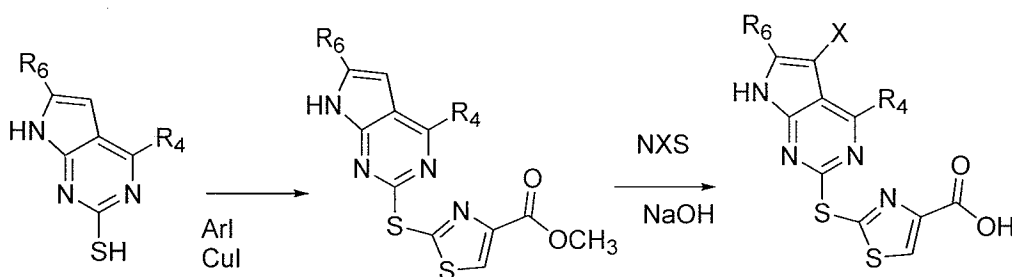
1-(4-(6-Ethyl-2-(pyridin-3-yloxy)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazin-1-yl)ethanone

[0162] 2,4-dichloro-6-ethyl-7H-pyrrolo[2,3-d]pyrimidine (Example 51) (100 mg, 0.46 mmol) was combined with potassium carbonate (80 mg, 0.5 mmol), 1-acetylpiperazine (59 mg, 0.46 mmol), NMP (5 mL). The reaction was purged of oxygen with a dry stream of nitrogen and microwave heated to 120°C for 10 min. The NMP was removed by rotary

evaporator and the crude product was purified by HPLC. A white solid product was obtained (92 mg), LCMS: 308.11.

[0163] The above compound (80 mg, 0.26 mmol) was combined with potassium fluoride (75 mg, 1.3 mmol) and dry acetone (10 mL). The reaction was stirred at RT for 72 hr. The solvent was removed by rotary evaporator. The residues was combined with potassium carbonate (80 mg, 0.5 mmol), 3-hydroxy pyridine (50 mg, 0.52 mmol), NMP (5 mL). The reaction was purged of oxygen with a dry stream of nitrogen and microwave heated to 180°C for 10 min. The NMP was removed by rotary evaporator and the crude product was purified by HPLC. A white solid product was obtained (40 mg), LCMS: 367.28.

[0164] Various R⁴ groups may contain functionality that can be further elaborated to create additional analogs as demonstrated by Examples 56-62.



EXAMPLE 56

Methyl 2-(4-ethoxy-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)thiazole-4-carboxylate

[0165] 4-Ethoxy-6-ethyl-7H-pyrrolo[2,3-d]pyrimidine-2-thiol (100 mg, 0.448 mmol) and methyl 2-bromothiazole-4-carboxylate (104 mg, 0.470 mmol) were added to glacial AcOH (1.5 mL) and the mixture was stirred at 90°C for 1 h. The mixture was then added to a stirred solution of NaHCO₃ and the precipitated methyl 2-(4-ethoxy-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)thiazole-4-carboxylate (60 mg, 0.165 mmol, 36.8% yield) was collected by filtration.

EXAMPLE 57

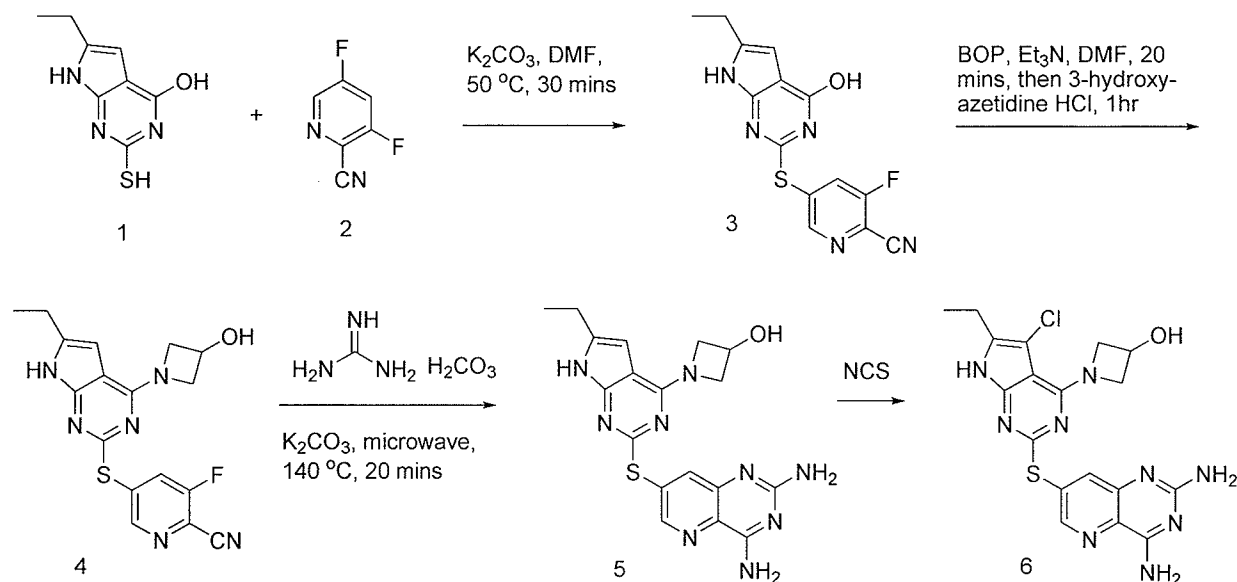
Methyl 2-(5-bromo-4-ethoxy-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)thiazole-4-carboxylate

[0166] Methyl 2-(4-ethoxy-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)thiazole-4-carboxylate (Example 40) (40 mg, 0.110 mmol) was dissolved in NMP (0.5 mL) and NBS (N-bromosuccinimide) (19.53 mg, 0.110 mmol) was added at 0°C. The mixture was stirred at

23°C for 10min. Methanol (0.5 mL) was added and the mixture was purified by HPLC to obtain methyl 2-(5-bromo-4-ethoxy-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)thiazole-4-carboxylate (15 mg, 0.034 mmol, 30.8% yield). LC-MS 445 (M+H).

EXAMPLE 58

2-(5-bromo-4-ethoxy-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)thiazole-4-carboxylic acid
[0167] Methyl 2-(5-bromo-4-ethoxy-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)thiazole-4-carboxylate (Example 42) (10 mg, 0.023 mmol) and 2 M sodium hydroxide (90 μ L, 0.180 mmol) were stirred for 3min at 90°C in a mixture of MeOH (0.5 mL) and NMP (0.5 mL) and then stirred for further 30min at 23°C. The reaction mixture was purified by HPLC to obtain 2-(5-bromo-4-ethoxy-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)thiazole-4-carboxylic acid (7 mg, 0.016 mmol, 72.3% yield).



EXAMPLE 59

5-(6-ethyl-4-hydroxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)-3-fluoropicolinonitrile

[0168] 6-ethyl-2-mercapto-7H-pyrrolo[2,3-d]pyrimidin-4-ol (Example 2) (98 mg, 0.5 mmol) and 2-cyano-3,5-difluoropyridine (70.1 mg, 0.5 mmol) were combined with potassium carbonate (276.5 mg, 2 mmol) and DMF (2 mL). The reaction was heated at 50°C for 30 minutes. It was then cooled to room temperature and the solid was filtered off. The product solution was carried on to the next step without purification.

EXAMPLE 60

5-(6-ethyl-4-(3-hydroxyazetidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)-3-fluoropicolinonitrile

[0169] To the above solution of 5-(6-ethyl-4-hydroxy-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)-3-fluoropicolinonitrile was added [benzotriazole-1-yl-oxy-tris-(dimethylamino)phosphonium hexafluorophosphate] (265.4 mg, 0.6 mmol) and triethylamine (0.5 mL). After stirred at room temperature for 20 minutes, the mixture was added with 3-hydroxyazetidine HCl (200 mg, 2 mmol). The reaction was completed in 1 hour at room temperature. The product was purified by column chromatography (100% ethyl acetate).

EXAMPLE 61

1-(2-(2,4-diaminopyrido[2,3-d]pyrimidin-6-ylthio)-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-ol

[0170] 5-(6-ethyl-4-(3-hydroxyazetidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)-3-fluoropicolinonitrile (Example 60) (50 mg, 0.135 mmol) was combined with guanidine carbonate (90.1 mg, 0.5 mmol), potassium carbonate (138.3 mg, 1 mmol), and DMF (2 mL). The reaction was heated at 140°C under microwave condition for 20 minutes. The mixture was then purified by high performance liquid chromatography to yield the desired product.

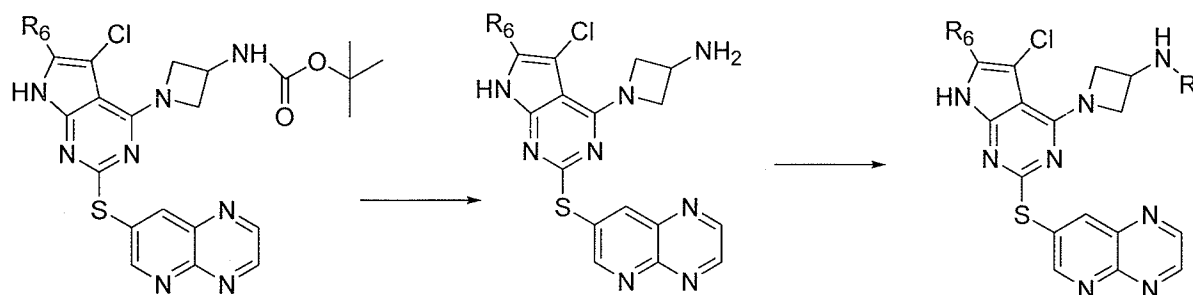
EXAMPLE 62

1-(5-chloro-2-(2,4-diaminopyrido[2,3-d]pyrimidin-6-ylthio)-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-ol

[0171] To a solution of 1-(2-(2,4-diaminopyrido[2,3-d]pyrimidin-6-ylthio)-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-ol (Example 61) (10.24 mg, 0.025 mmol) in THF (1 mL) was added drop-wise a solution of N-chlorosuccinimide (6.8 mg, 0.05 mmol) in DMF (0.5 mL). The reaction was warmed in a 50°C water bath for 1 minute. The water bath was removed, and the reaction was allowed to stir for another 5 minutes and monitored by LCMS. The warm-up process was repeated if necessary to complete the reaction. The completed reaction was cooled in an iced-water bath and quenched with methanol (0.5 mL). Upon HPLC purification, 1-(5-chloro-2-(2,4-diaminopyrido[2,3-d]pyrimidin-6-ylthio)-6-

ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-ol was obtained as the white solid TFA salt.

[0172] Various R^2 groups may contain functionality that can be further elaborated to create additional analogs as demonstrated by Examples 63-65.



EXAMPLE 63

1-(5-chloro-6-ethyl-2-(pyrido[3,2-b]pyrazin-7-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-amine

[0173] Tert-butyl 1-(5-chloro-6-ethyl-2-(pyrido[3,2-b]pyrazin-7-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-ylcarbamate (800 mg, 1.559 mmol) was added to DCM (20 mL) and the mixture was cooled to 0°C. TFA (5 mL) was added and the mixture was stirred at 40°C for 1 h. The mixture was then added to rapidly stirring diethyl ether and the precipitated TFA salt of 1-(5-chloro-6-ethyl-2-(pyrido[3,2-b]pyrazin-7-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-amine (650 mg, 1.234 mmol, 79% yield) was collected by filtration under nitrogen.

EXAMPLE 64

N-(1-(5-chloro-6-ethyl-2-(pyrido[3,2-b]pyrazin-7-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-yl)methanesulfonamide

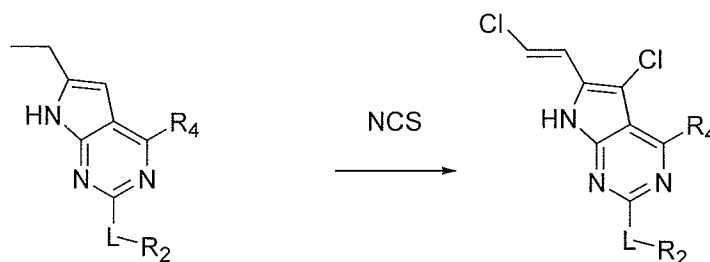
[0174] To a stirred solution of 1-(5-chloro-6-ethyl-2-(pyrido[3,2-b]pyrazin-7-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-amine (Example 63) (20 mg, 0.048 mmol) and triethylamine (20.25 μ L, 0.145 mmol) in NMP (0.7 mL) was added methanesulfonyl chloride (5.55 mg, 0.048 mmol) at 0°C and the mixture was stirred at 23°C for 2 h. MeOH (0.5 mL) was added and the mixture was purified by HPLC to obtain N-(1-(5-chloro-6-ethyl-2-(pyrido[3,2-b]pyrazin-7-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-yl)methanesulfonamide (11 mg, 0.022 mmol, 46.3% yield).

EXAMPLE 65

N-(1-(5-chloro-6-ethyl-2-(pyrido[3,2-b]pyrazin-7-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-yl)-1H-imidazole-5-carboxamide

[0175] To a mixture of 1-(5-chloro-6-ethyl-2-(pyrido[3,2-b]pyrazin-7-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-amine (Example 63) (20 mg, 0.048 mmol), 1H-imidazole-5-carboxylic acid (6.52 mg, 0.058 mmol) and BOP (25.7 mg, 0.058 mmol) in NMP (0.7 mL) was added triethylamine (20.25 μ l, 0.145 mmol) at 0°C and the mixture was stirred at 23°C for 2 h. MeOH (0.5 mL) was added and the mixture was purified by HPLC to obtain N-(1-(5-chloro-6-ethyl-2-(pyrido[3,2-b]pyrazin-7-ylthio)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)azetidin-3-yl)-1H-imidazole-5-carboxamide (9 mg, 0.018 mmol, 36.6% yield).

[0176] The R⁶ ethyl group can be converted to a chlorovinyl group by using multiple equivalents of NCS as shown in Example 66.

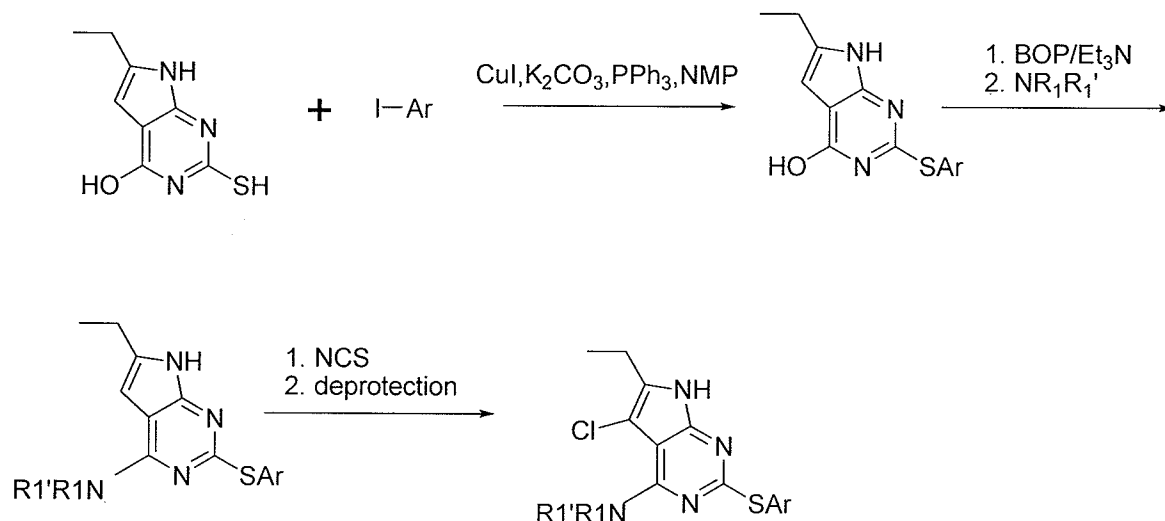


EXAMPLE 66

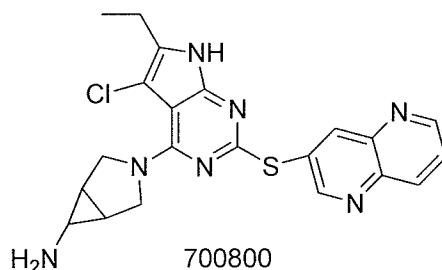
(E)-methyl 2-(5-chloro-6-(2-chlorovinyl)-4-(3-(pyrimidin-2-ylmethyl)azetidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)thiazole-4-carboxylate

[0177] Methyl 2-(6-ethyl-4-(3-(pyrimidin-2-ylmethyl)azetidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)thiazole-4-carboxylate (50 mg, 0.1 mmol) was combined with NCS (21 mg, 0.15 mmol), NMP (5 mL). The reaction was stirred at room temperature overnight. The NMP was removed by rotary evaporator and the crude product was purified by HPLC. A white solid product (3) was obtained (18 mg), LCMS: 468.05. product (4) (15 mg), LCMS: 522.00.

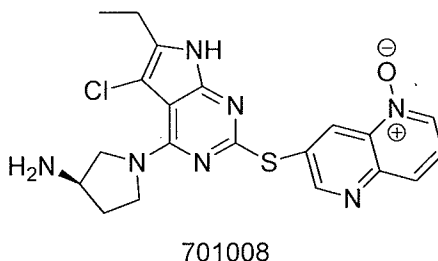
EXAMPLE 67 GENERAL SYNTHESIS METHOD OF S-LINKED COMPOUNDS



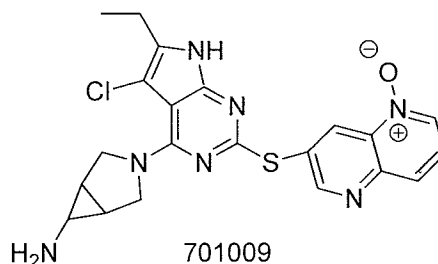
[0178] The solution of CuI (67 mg, 0.35 mmol), *N,N'*-dimethylcyclohexane-1,2-diamine (100 mg, 0.70 mmol) in 9 mL of NMP was added to a stirring suspension of him and (Example 2) (229 mg, 1.17 mmol), a proper I-Ar (1.17 mmol), K₂CO₃ (324 mg, 2.35 mmol) and PPh₃ (400 mg, 1.53 mmol) in NMP (9 mL). The mixture was heated to 130 °C for 2 to 12 hrs monitored by LC-MS for the completion of the reaction. When the reaction completed, the mixture was cooled to 0 °C, BOP (621 mg, 1.40 mmol) and Et₃N (0.41 mL, 2.93 mmol) was added, stirred for 30 minutes at 0 °C, then warmed up to room temperature, a suitable Boc-protected diamine (2.34 mmol) was added. The reaction mixture was heated to 50 °C for 30 minutes. LC-MS indicated the completed reaction. At room temperature, N-chlorosuccinimide (NCS, 156 mg, 1.17 mmol) was added in several portions. The mixture was stirred for 2 to 12 hrs for the completion of the reaction, heated to 40 °C if the reaction failed to proceed. TFA was finally added to the mixture to remove the Boc protection group. After removal of solvents, Prep HPLC of the resulting residue (eluent: CH₃CN/H₂O/0.1%TFA) to give the desired S-linked compounds, such as those identified below. R1 and R1' in the above scheme together refer to the remainder of an amine-containing moiety, such as the heteralicyclic groups shown in the compounds below.



3-(2-(1,5-naphthyridin-3-ylthio)-5-chloro-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-3-azabicyclo[3.1.0]hexan-6-amine



(R)-7-(4-(3-aminopyrrolidin-1-yl)-5-chloro-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)-1,5-naphthyridine 1-oxide



7-(4-(6-amino-3-azabicyclo[3.1.0]hexan-3-yl)-5-chloro-6-ethyl-7H-pyrrolo[2,3-d]pyrimidin-2-ylthio)-1,5-naphthyridine 1-oxide

Determination of anti-bacterial efficacy

[0179] Colonies of *H. influenzae*, *E. coli*, *S. aureus*, *A. baumannii*, *S. pneumoniae*, *P. aeruginosa*, and *B. thailandensis* were picked from o/n plates and resuspended in 3ml DPBS solution. Absorbance was read at 600nm and solutions were diluted to an OD of 0.1. Inoculums were added to appropriate growth media, and 98ul of the mixture was plated into columns 1-11 of a 96 well flat-bottomed cell-culture plate. Column 12 was plated with media only. 2uL of compound dilution series in 100% DMSO were added to columns 1-10. Plates were agitated in plate-shaker for 1min. Mixtures of cells and media were diluted 1000x in DPBS and 100uL was plated onto appropriate media and

incubated o/n in order to count CFUs. Plates were incubated o/n at 35C. *H. influenzae* and *S. pneumoniae* plates were incubated with 5% CO₂. 10uL of Alamar Blue (Invitrogen) was added to plates, and plates were agitated for 1min in plate-shaker. Plates were incubated at 35C for 1h. Plates were read by eye, with any change in color from blue read as alive.

TABLE OF BACTERIAL STRAINS AND MEDIA USED

		Resuspended Cells	Media
<i>S. aureus</i>	ATCC 13709	50uL	20mL MHCA
<i>SA</i> + serum	ATCC 13709	50uL	16mL MHCA + 4mL mouse serum
<i>S. pneumoniae</i>	ATCC 51916	200uL	20mL MHCA + 3% Laked Horse Blood
<i>H. influenzae</i>	ATCC 49247	50uL	20mL haemophilus test media
<i>E. coli</i> 8	ATCC 25922	100uL	20mL MHCA
<i>EC8</i> + serum	ATCC 25922	100uL	16mL MHCA + 4mL mouse serum
<i>E. coli</i> 9	ATCC 35218	100uL	20mL Mueller Hinton cationic adjusted
<i>E. coli imp</i>	Benson BAS849	100uL	20mL MHCA
<i>E. coli ΔtolC</i>	BW25113 <i>ΔtolC</i>	100uL	20mL MHCA
<i>B. thailandensis</i>	ATCC E264	100uL	20mL MHCA
<i>P. aeruginosa</i>	ATCC 15692	100uL	20mL MHCA
<i>A. baumannii</i>	ATCC 19606	50uL	20mL MHCA

Antibacterial Potency MIC (μg/mL)			
compound	701800	701008	701009
<i>S. aureus</i>	≤0.5	≤0.5	≤0.5
<i>S. aureus</i> + serum*	1	≤0.5	≤0.5
<i>S. pneumoniae</i>	≤0.5	1	≤0.5
<i>H. influenzae</i>	4	2	2
<i>E. coli</i> (wt)	4	4	2
<i>E. coli</i> + serum*	8	2	4
<i>E. coli</i> (tolC)**	≤0.5	≤0.5	≤0.5
<i>E. coli</i> (Imp)***	1	1	≤0.5

Antibacterial Potency MIC ($\mu\text{g/mL}$)			
compound	701800	701008	701009
<i>K. pneumoniae</i> 11	>64	32	32
<i>K. pneumoniae</i> 101	≤ 0.5	≤ 0.5	≤ 0.5
<i>A. baumannii</i>	8	8	4
<i>P. aeruginosa</i> (wt)	8	16	4

Serum* = 20% mouse serum

tolC** = pump knock-out

Imp*** = permeability mutant

[0180] Table 2 illustrates various compounds' bacterial efficacy against *S. aureus*, *S. pneumoniae* and *E. coli* 8 by listing MIC (Minimum Inhibitory Concentration) data.

ATPase enzymatic assay

[0181] DNA gyrase B activities were determined by following the gyrase B-dependent release of inorganic phosphate from ATP hydrolysis and subsequent detection through use of a 7-methyl-6-thioguanosine/phosphorylase spectrophotometric assay. Assays were performed in 25 mM Tris-HCl buffer (pH 7.9), 5 mM MgCl_2 , and 200 mM NaCl, 0.2 mM 7-methyl-6-thioguanosine, purine nucleoside phosphorylase (1 unit/mL), 0.4 mM ATP and various concentrations of the inhibitor compounds prepared in Me_2SO . The final Me_2SO concentration in each reaction was 2%. The compounds were assayed against full length protein from *Enterococcus faecalis* and *Acinetobacter baumannii*. The concentration of enzyme in the assay ranged from 60 nM for *E. faecalis* full-length gyrase B to 200 nM for *A. baumannii* full-length Gyrase B. Reactions were initiated with the addition of ATP, and monitored at 360 nm at room temperature for 30 min.

ATPase assay:

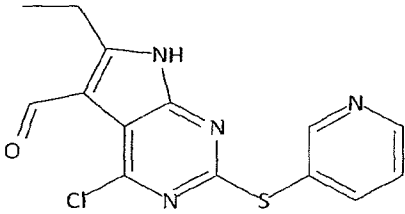
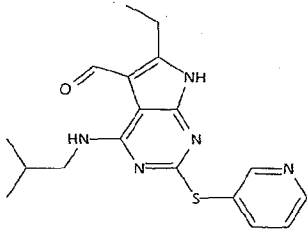
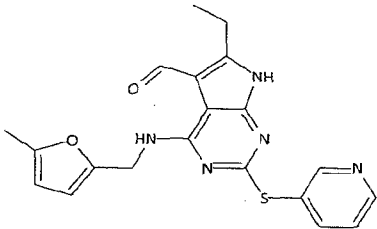
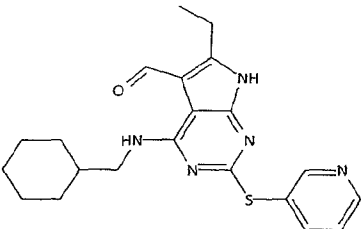
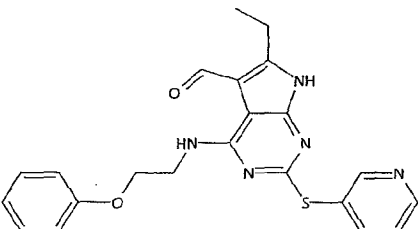
[0182] ATPase activities of all DNA Gyrase B and Topoisomerase IV parE were determined through use of a coupled spectrophotometric assay in which the enzyme-dependent release of inorganic phosphate from ATP hydrolysis is measured. The assay comprises between 20-100 nM GyrB or parE (active site concentrations) in 50 mM Tris-HCl buffer (pH 7.6), 2 mM MgCl₂, 125 mM NaCl, 0.2 mM 7-methyl-6-thioguanosine, 1 U/ml purine nucleoside phosphorylase. The reaction is initiated by addition of ATP between 0.5 and 4 mM ATP and monitored at 360 nm for 30 min at 27°C. Inhibitor potency is determined by incubating the target enzyme in the presence of various concentrations of inhibitor for 10 minutes prior to addition of substrate. The final concentration of DMSO is kept constant at 2.5% (v/v).

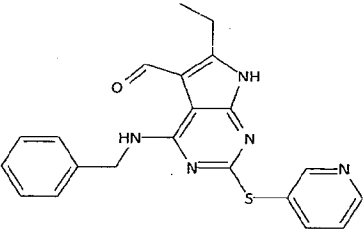
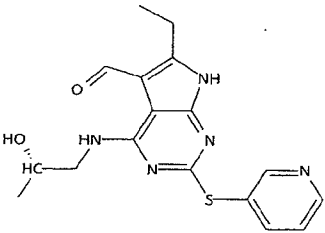
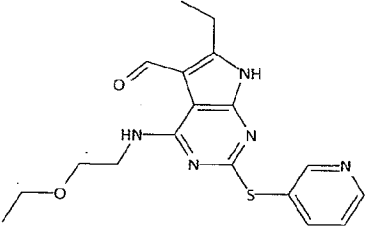
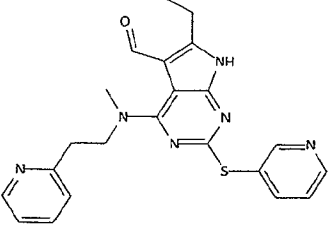
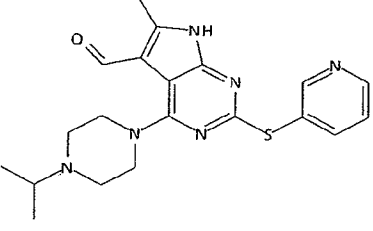
[0183] A wide range of wild-type and specific point-mutant full-length GyrB and parE enzyme were assayed, including, but not limited to, *E. faecalis*, *S.aureus*, *E.coli*, *F.tularencis*, *A.baumannii*, *H.influenzae*.

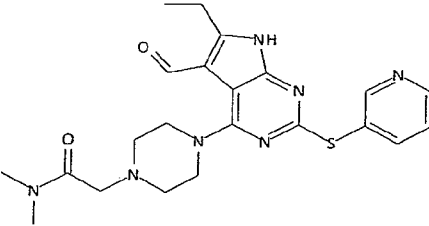
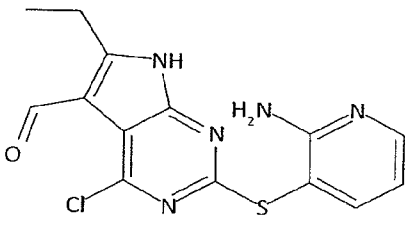
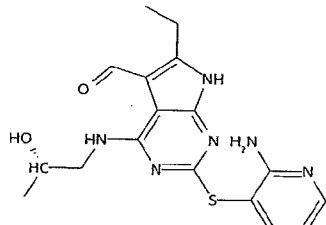
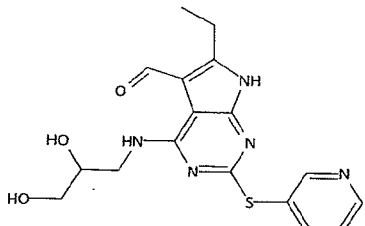
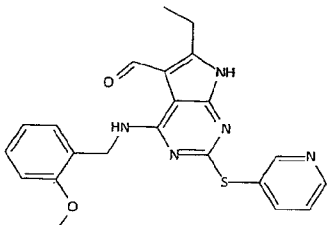
[0184] All enzymes were characterized for key kinetic parameter including K_m , k_{cat} and active site concentrations using standard methodologies.

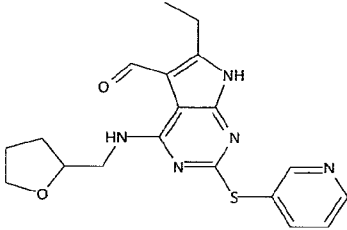
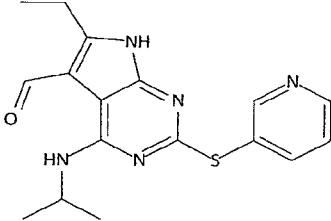
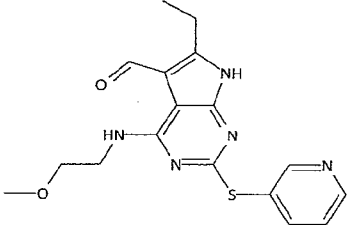
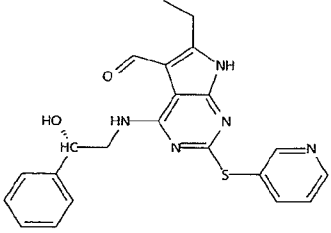
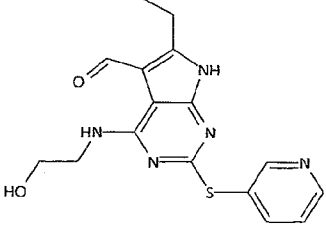
[0185] Kinetic analysis was carried out using using GraphPad Prism version 4.00 for Windows, GraphPad Software, San Diego California USA, on the world wide web at graphpad.com. K_i values were determined through use of the tight-binding kinetic analysis described in Morrison et al, *Biochem. Biophys. Acta*, **1969**, 185, 269-286.

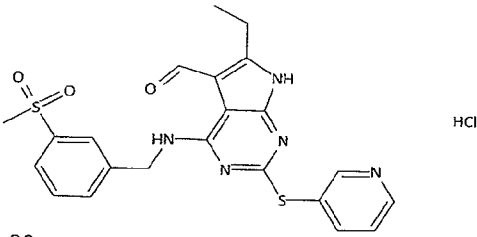
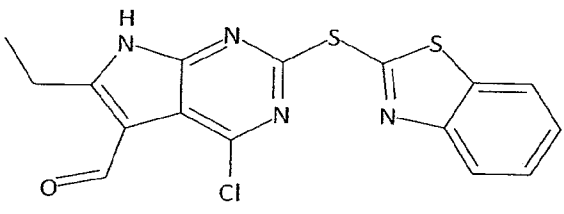
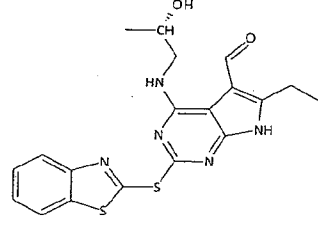
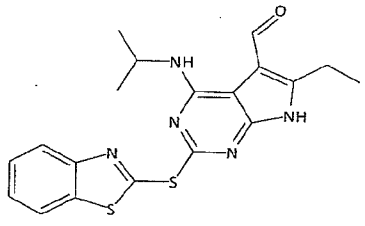
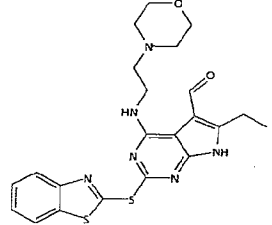
TABLE 1

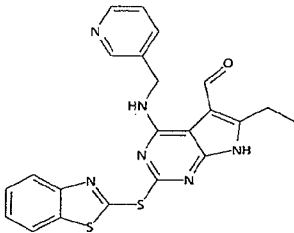
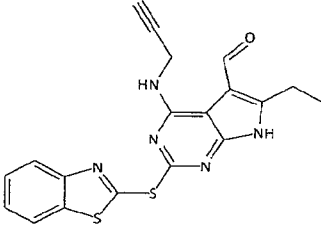
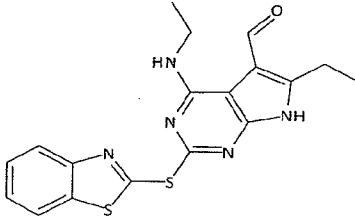
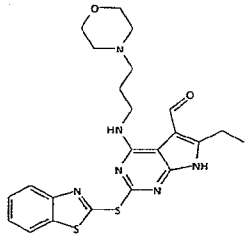
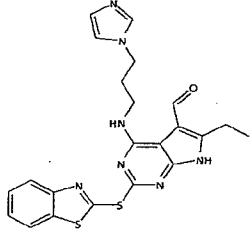
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700,077 Chemistry 2	
700,078 Chemistry 3	
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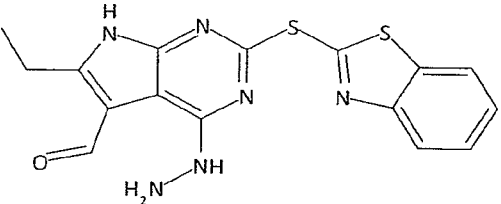
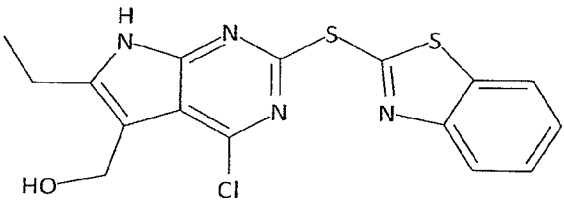
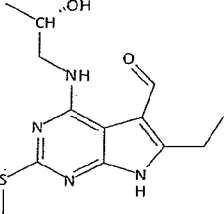
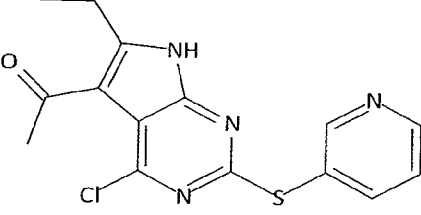
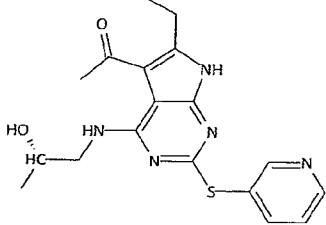
Rx ID	CHEMISTRY
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700,081	 <chem>CC1=C(C=CC(=O)N1C2=NC=NC(=C2)SC3=CC=CC=N3)N[C@H](C)O</chem>
700,082	 <chem>CC1=C(C=CC(=O)N1C2=NC=NC(=C2)SC3=CC=CC=N3)NCCCOCC</chem>
700,083	 <chem>CC1=C(C=CC(=O)N1C2=NC=NC(=C2)SC3=CC=CC=N3)N(C)CCCN4=CC=CC=N4</chem>
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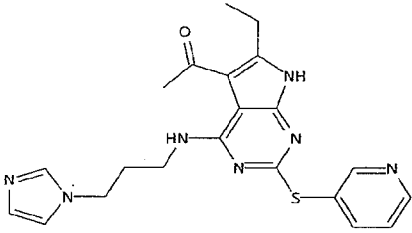
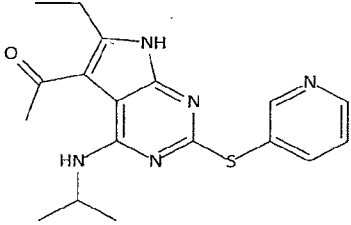
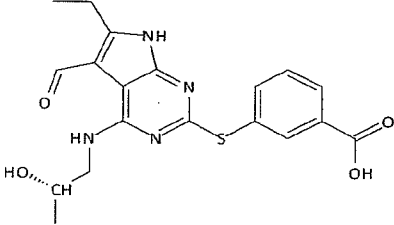
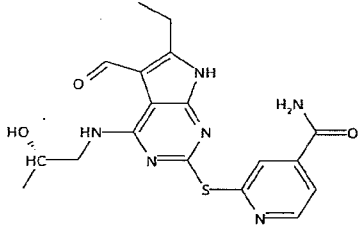
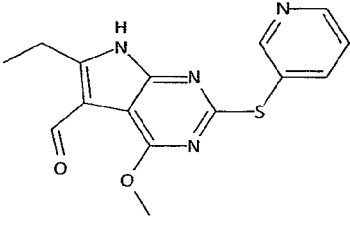
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700,088	 Chemistry 11
700,089	 Chemistry 12
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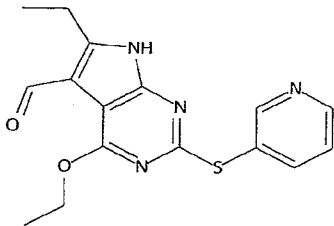
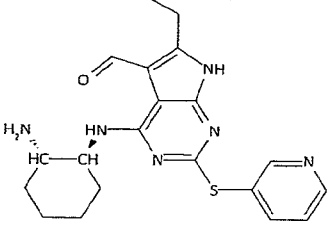
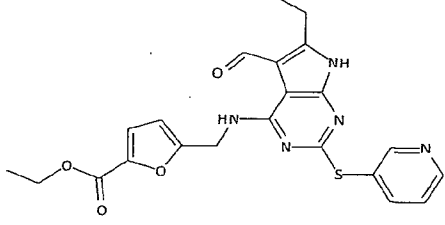
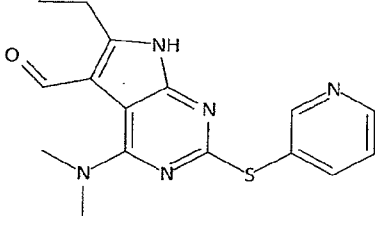
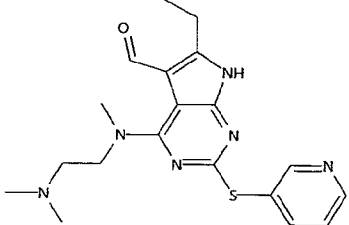
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700,096	 Chemistry 19

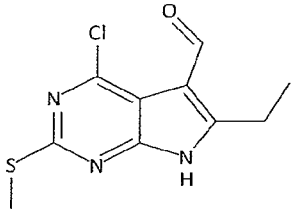
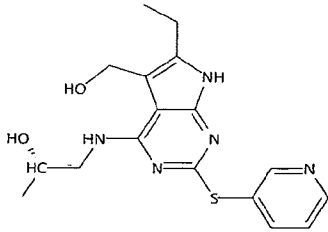
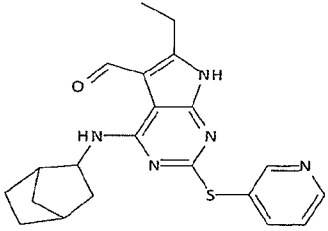
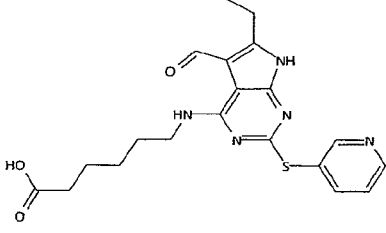
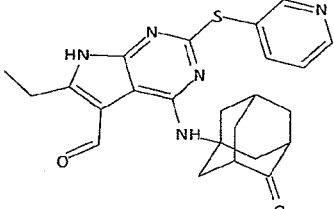
Rx ID	CHEMISTRY
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700,100	 Chemistry 22
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700,102	 Chemistry 24

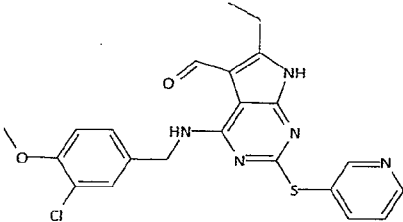
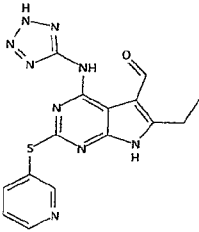
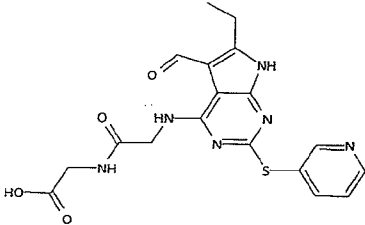
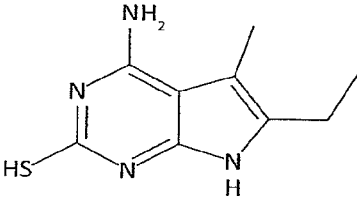
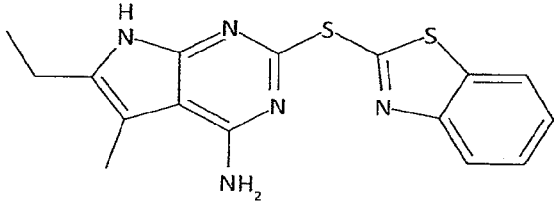
Rx ID	CHEMISTRY
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700,107	 Chemistry 29

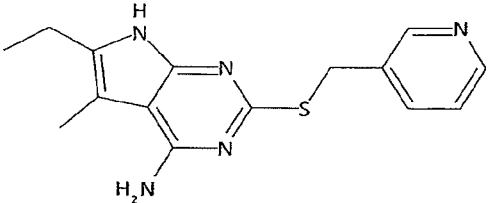
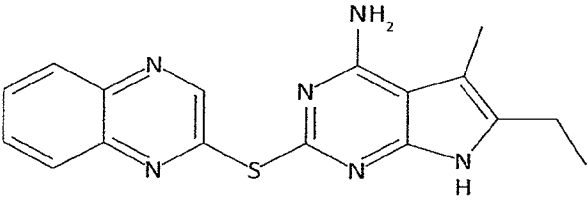
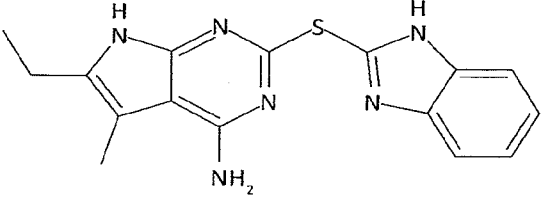
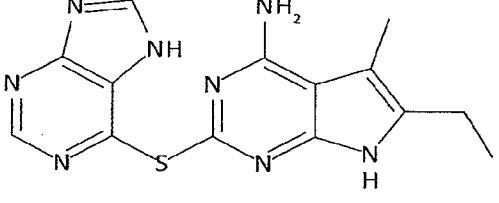
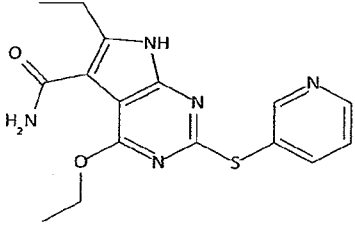
Rx ID	CHEMISTRY
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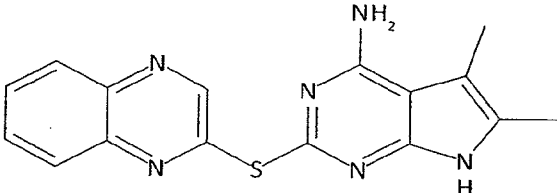
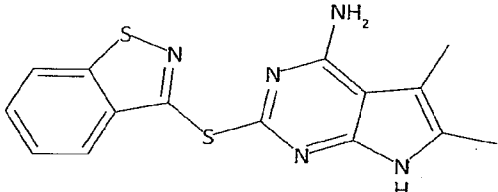
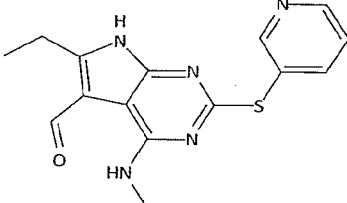
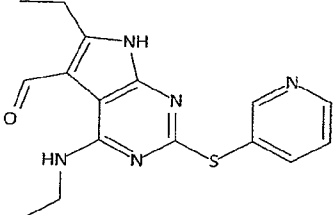
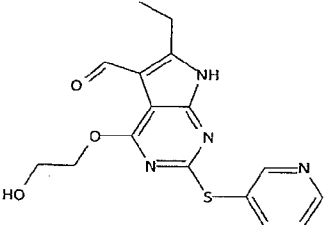
Rx ID	CHEMISTRY
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700,127	 Chemistry 37
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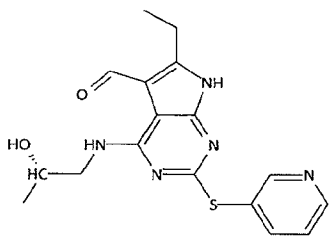
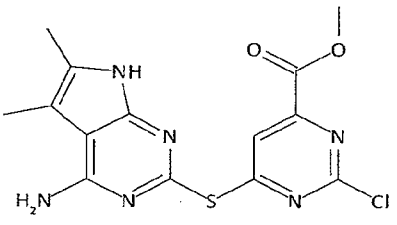
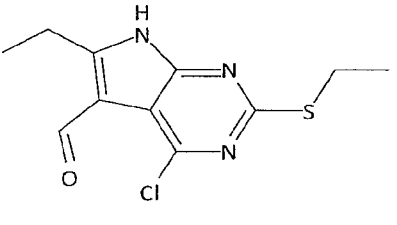
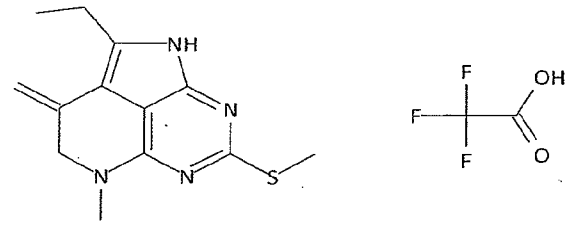
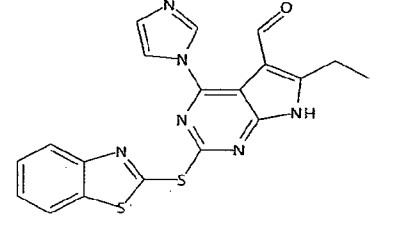
Rx ID	CHEMISTRY
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700,133	
700,135	
700,136	
700,137	

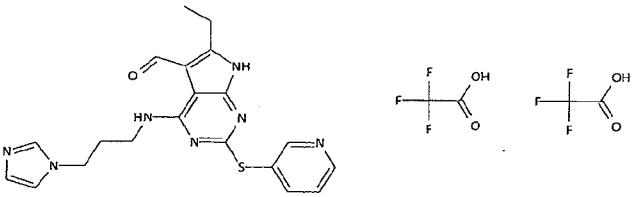
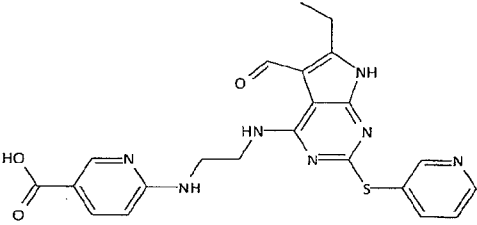
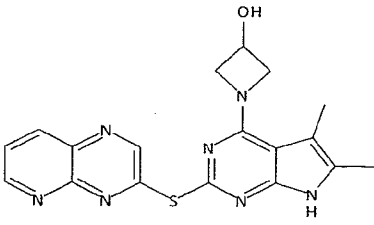
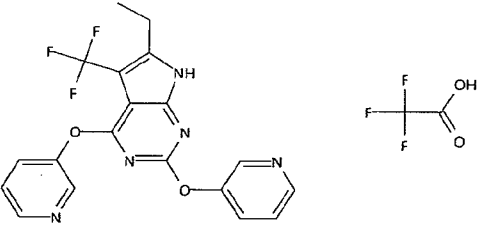
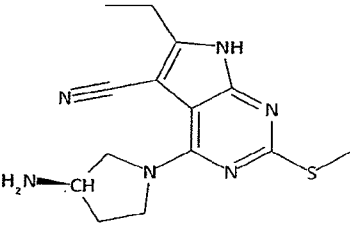
Rx ID	CHEMISTRY
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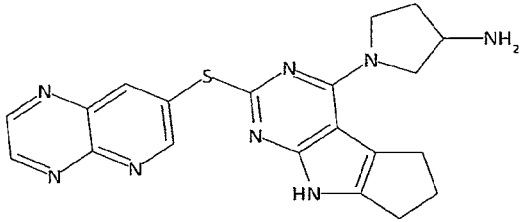
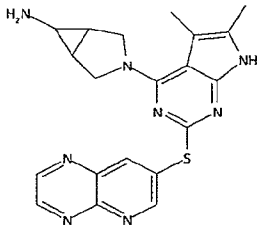
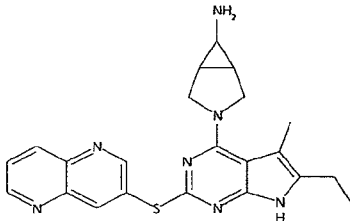
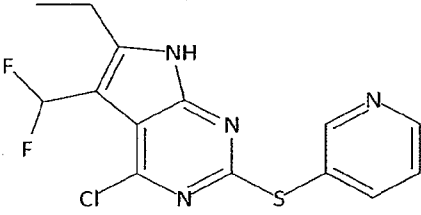
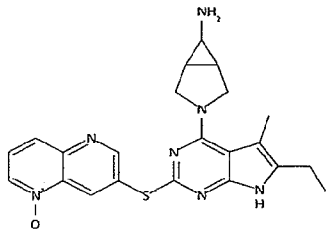
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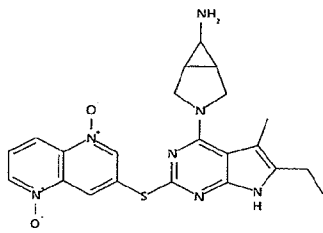
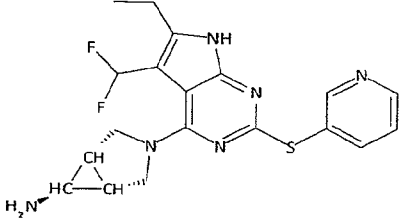
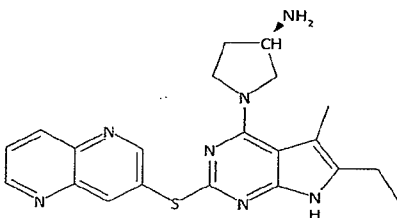
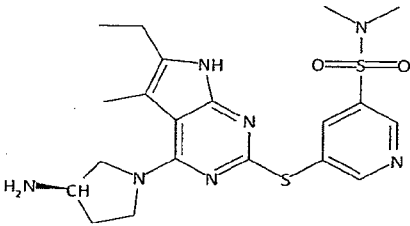
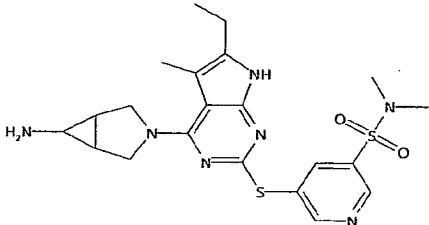
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700,152	 Chemistry 59

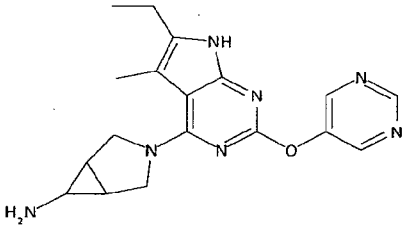
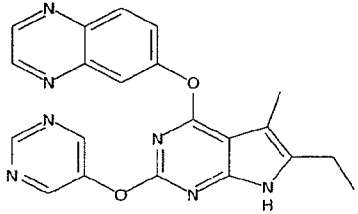
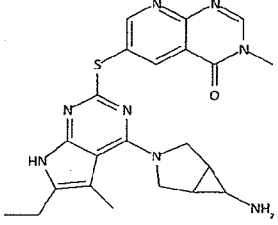
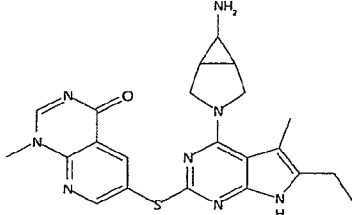
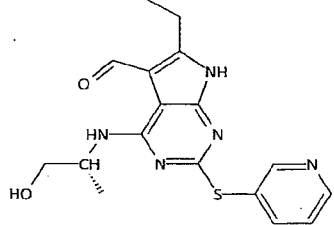
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700,155	 Chemistry 62
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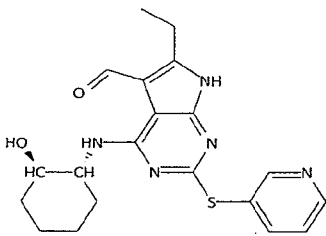
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700,159	
700,160	
700,244	
700,246	

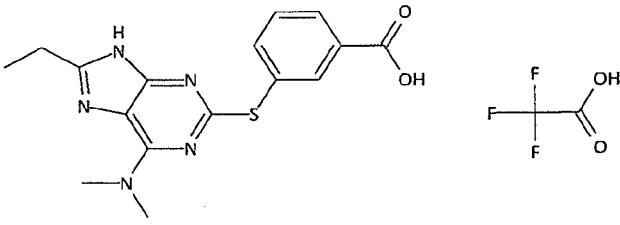
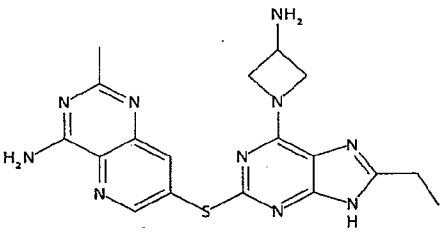
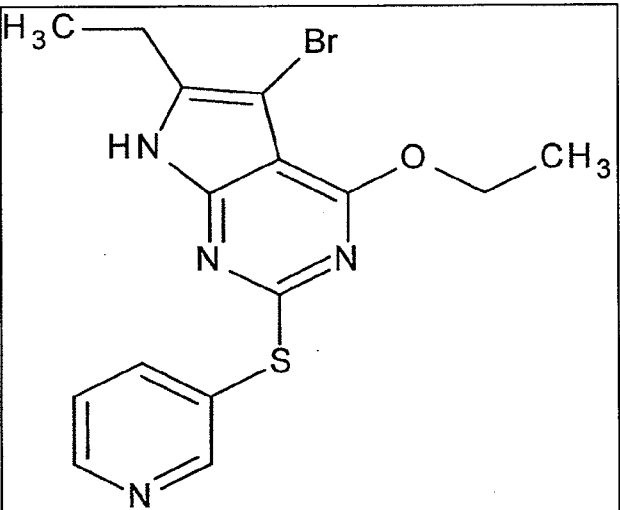
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701,077	 Chemistry 74

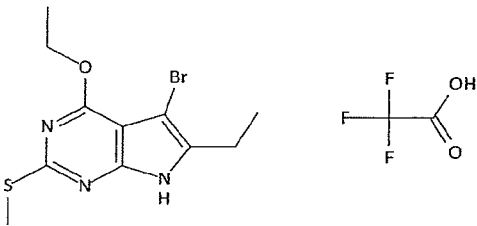
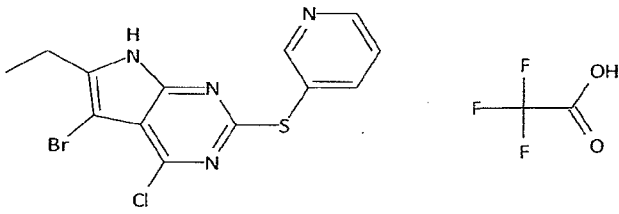
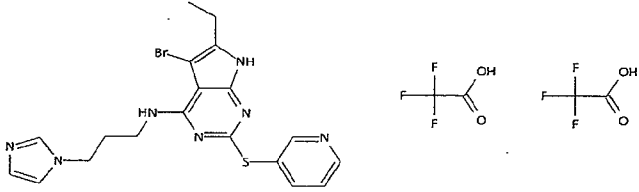
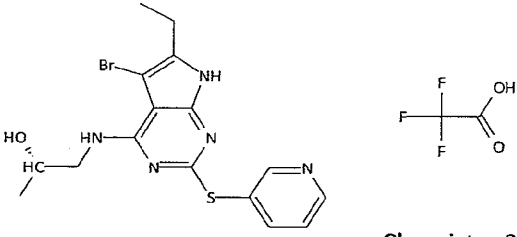
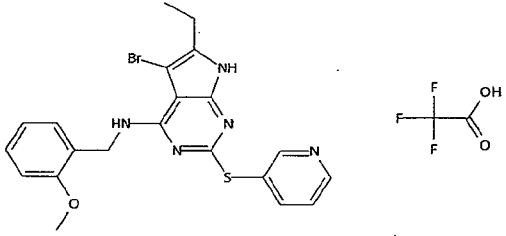
Rx ID	CHEMISTRY
7,011,092	
701,117	
701,143	
701,153	
701,156	

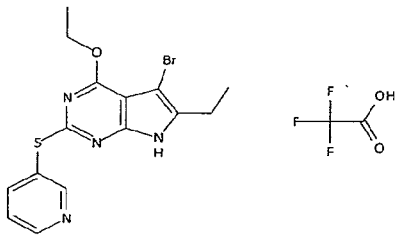
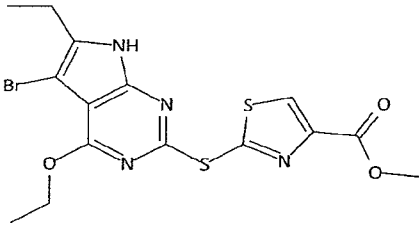
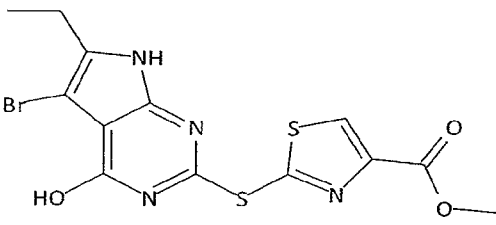
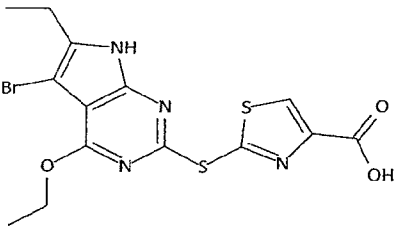
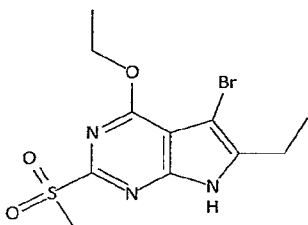
Rx ID	CHEMISTRY
701,157	 Chemistry 83
701,162	 Chemistry 84
701,161	 Chemistry 85
701,182	 Chemistry 86
701,183	 Chemistry 87

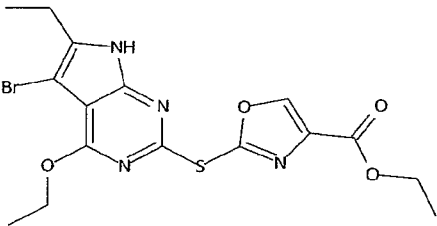
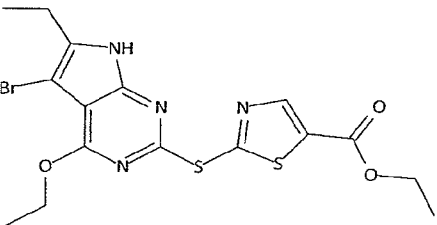
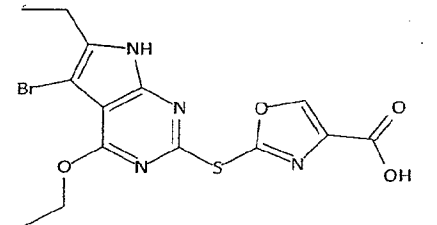
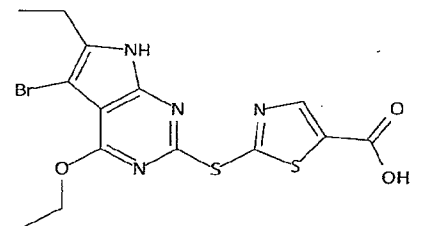
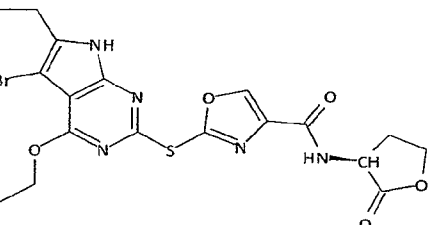
Rx ID	CHEMISTRY
701,193	 Chemistry 88
701,233	 Chemistry 89
701,239	 Chemistry 90
701,292	 Chemistry 91
700,131	 Chemistry 92

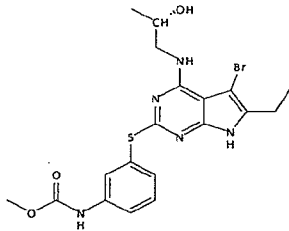
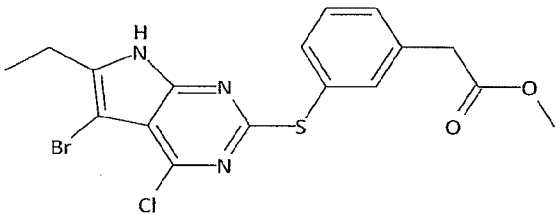
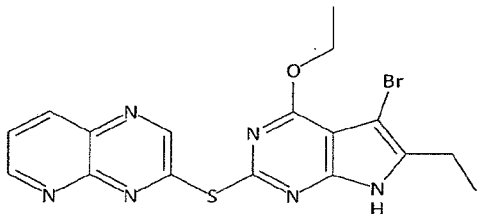
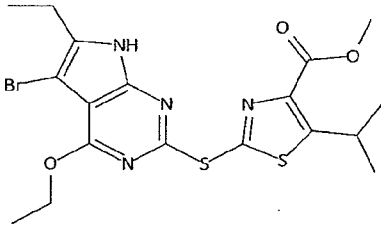
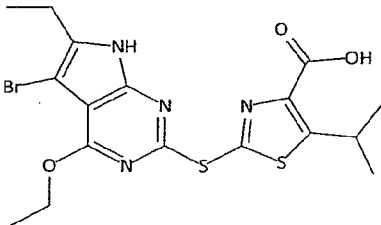
Rx ID	CHEMISTRY
700,132	 Chemistry 93

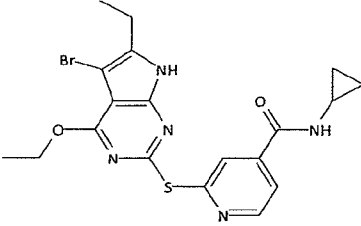
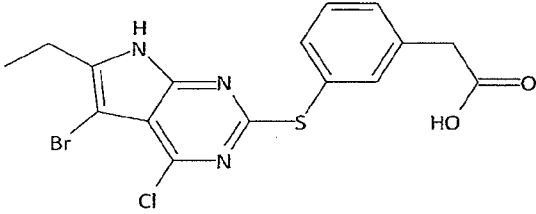
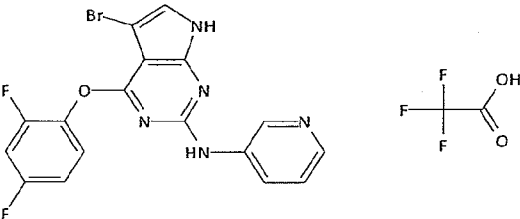
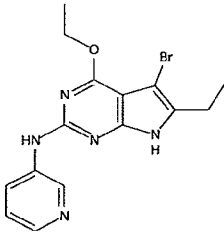
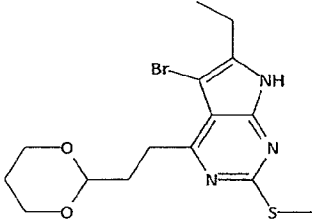
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700,220	
700,538	
700,280	

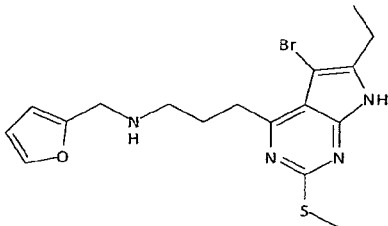
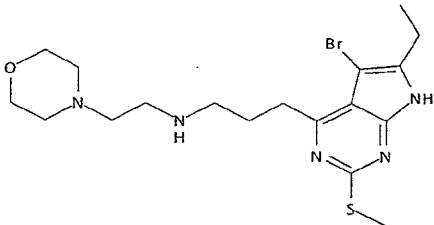
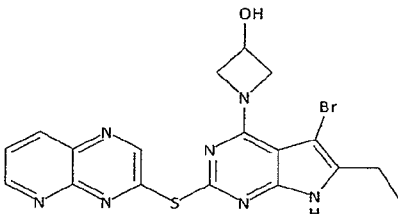
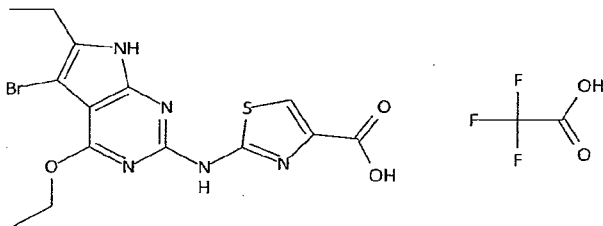
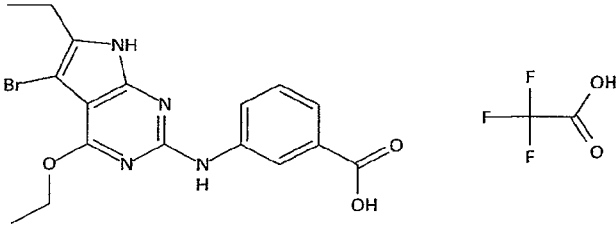
Rx ID	CHEMISTRY
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700,267	 Chemistry 1
700,269	 Chemistry 2
700,270	 Chemistry 3
700,271	 Chemistry 4

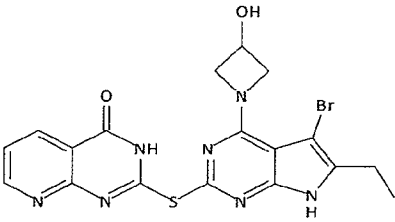
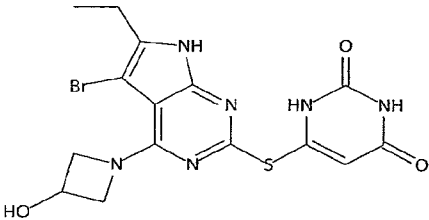
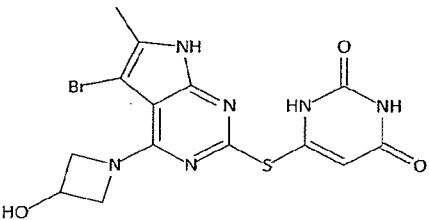
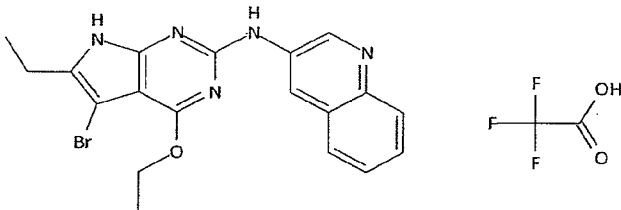
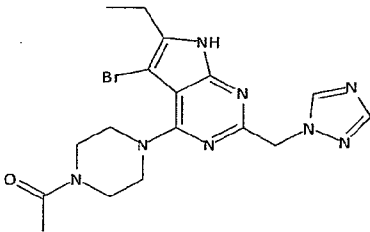
Rx ID	CHEMISTRY
700,275	 Chemistry 5
700,281	 Chemistry 6
700,282	 Chemistry 7
700,286	 Chemistry 8
700,288	 Chemistry 9

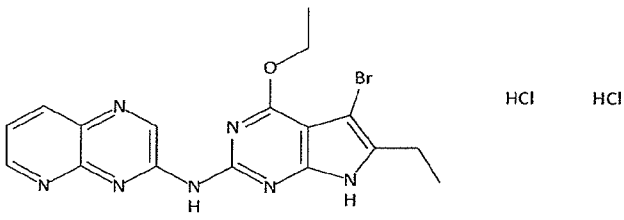
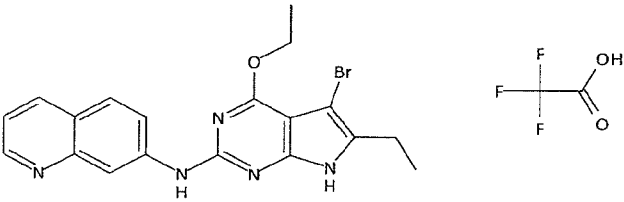
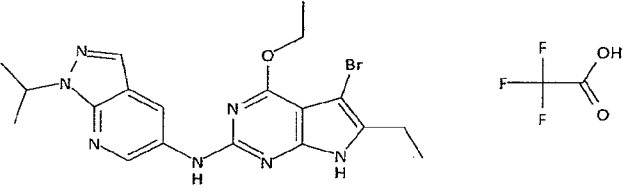
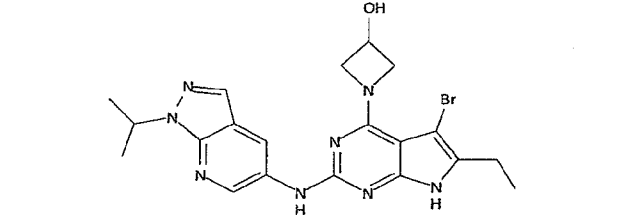
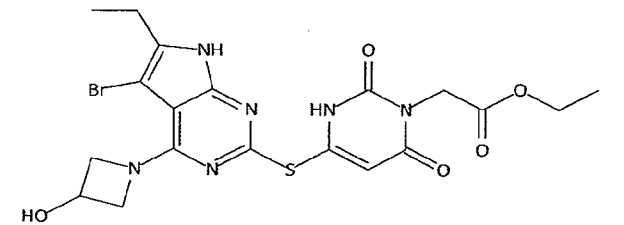
Rx ID	CHEMISTRY
700,290	 Chemistry 10
700,291	 Chemistry 11
700,292	 Chemistry 12
700,293	 Chemistry 13
700,294	 Chemistry 14

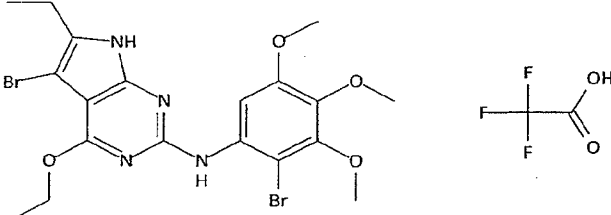
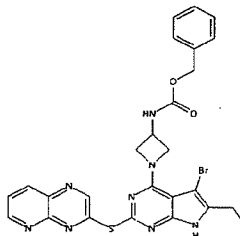
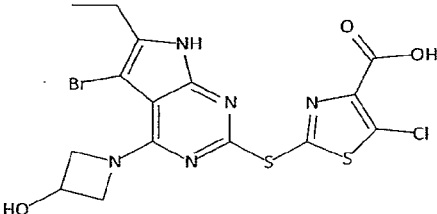
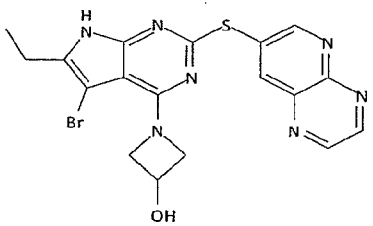
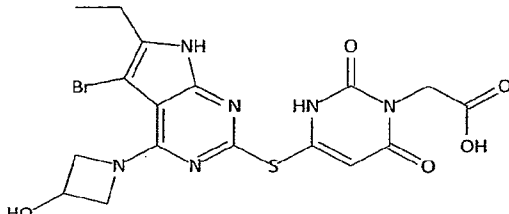
Rx ID	CHEMISTRY
700,295	 Chemistry 15
700,296	 Chemistry 16
700,297	 Chemistry 17
700,301	 Chemistry 18
700,303	 Chemistry 19

Rx ID	CHEMISTRY
700,305	 Chemistry 20
700,307	 Chemistry 21
700,315	 Chemistry 22
700,331	 Chemistry 23
700,332	 Chemistry 24

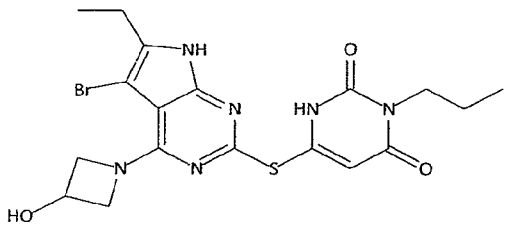
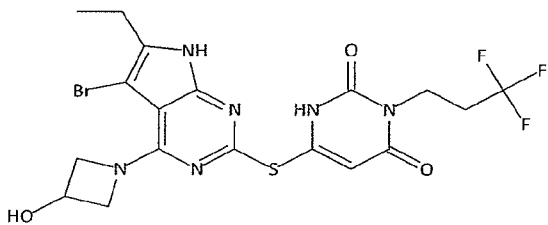
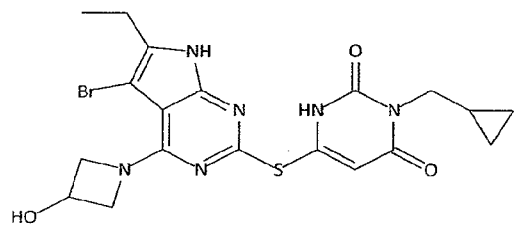
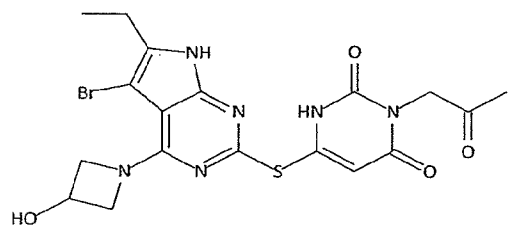
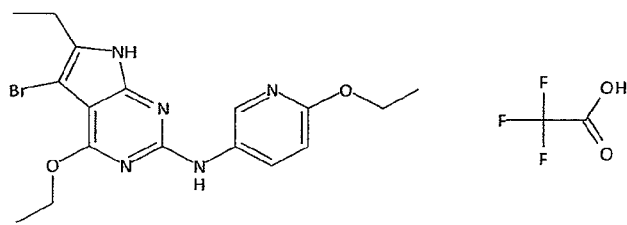
Rx ID	CHEMISTRY
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700,334	 Chemistry 26
700,346	 Chemistry 27
700,350	 Chemistry 28
700,354	 Chemistry 29

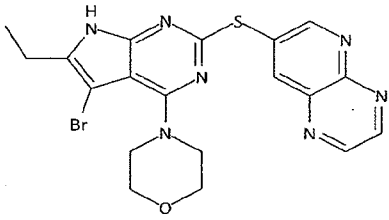
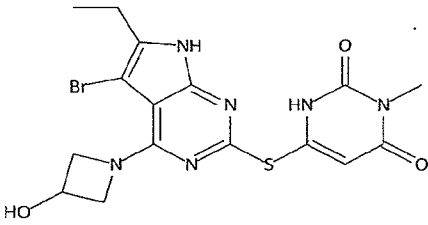
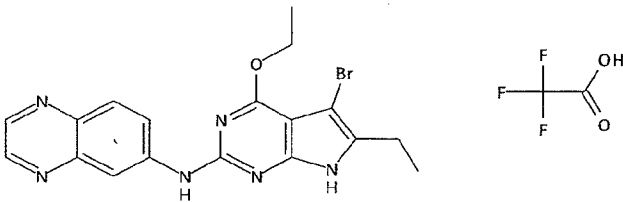
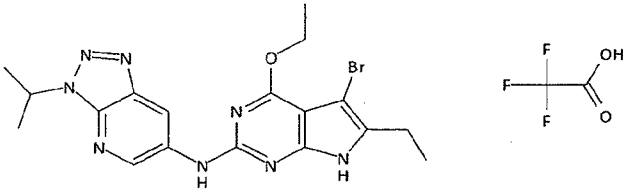
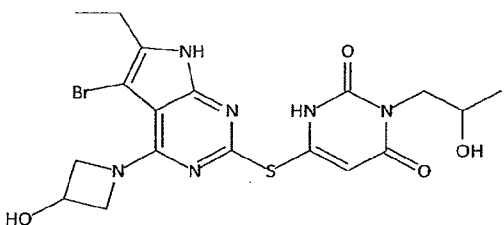
Rx ID	CHEMISTRY
700,358	 Chemistry 30
700,360	 Chemistry 31
700,362	 Chemistry 32
700,363	 Chemistry 33
700,374	 Chemistry 34

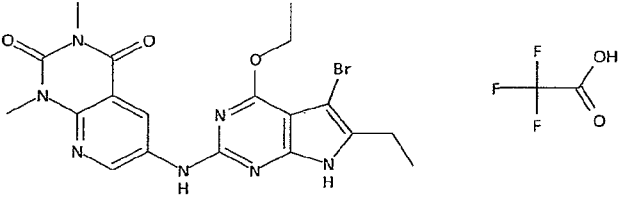
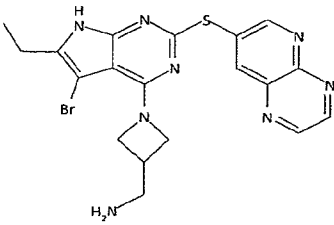
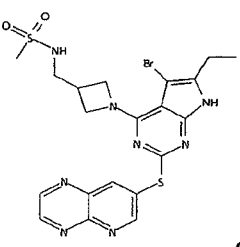
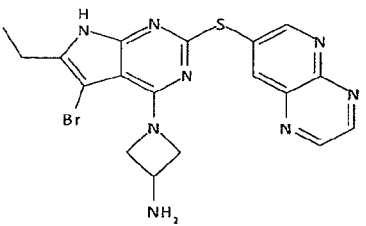
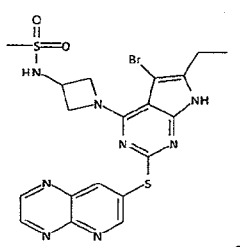
Rx ID	CHEMISTRY
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700,388	 Chemistry 36
700,381	 Chemistry 37
700,385	 Chemistry 38
700,386	 Chemistry 39

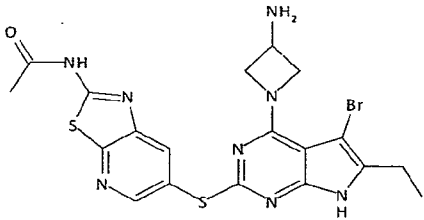
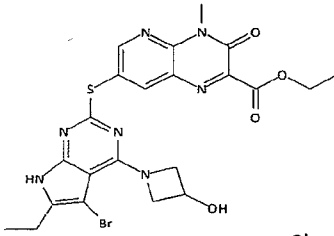
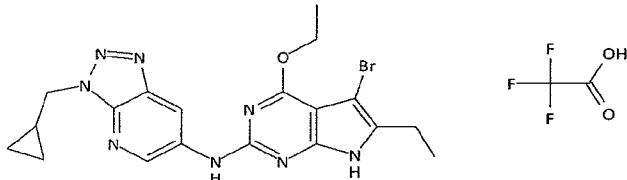
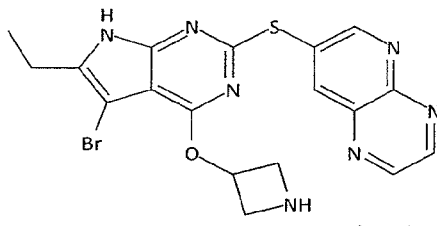
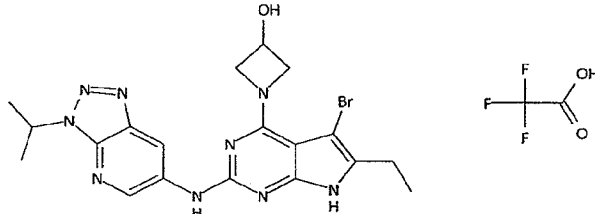
Rx ID	CHEMISTRY
700,389	 Chemistry 40
700,390	 Chemistry 41
700,391	 Chemistry 42
700,392	 Chemistry 43
700,402	 Chemistry 44

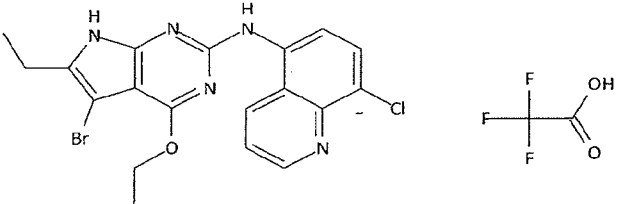
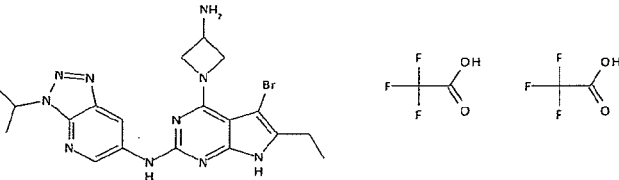
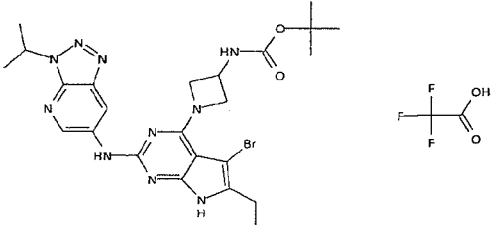
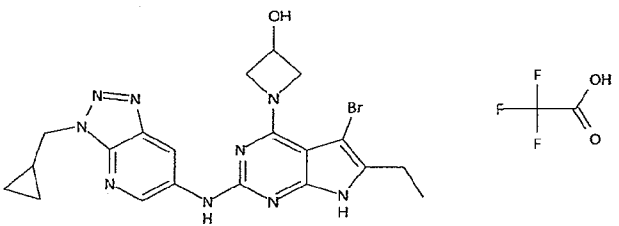
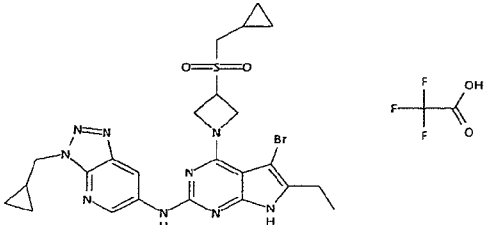
Rx ID	CHEMISTRY
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700,404	Chemistry 46
700,405	Chemistry 47
700,412	Chemistry 48
700,413	Chemistry 49

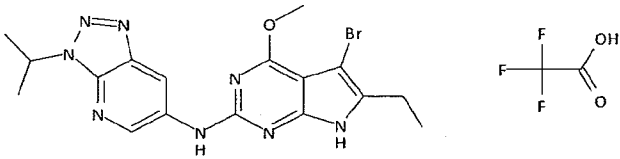
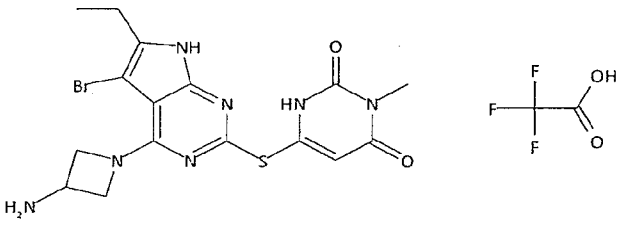
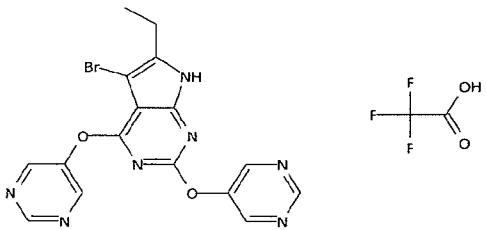
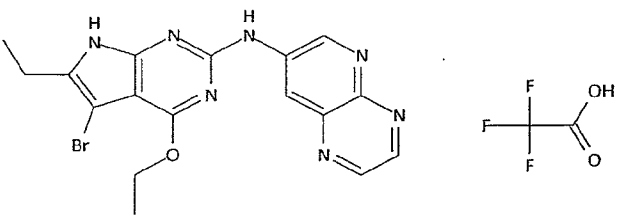
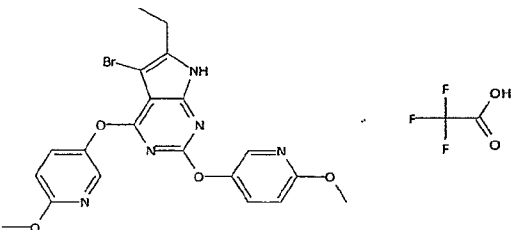
Rx ID	CHEMISTRY
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700,415	 Chemistry 51
700,416	 Chemistry 52
700,442	 Chemistry 53
700,417	 Chemistry 54

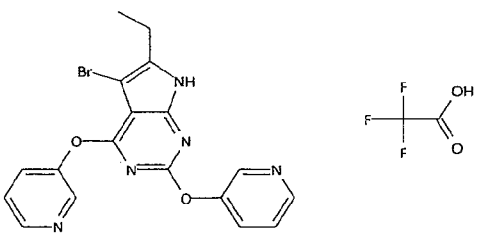
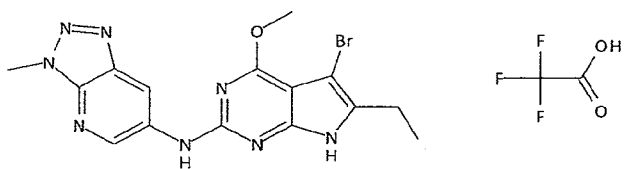
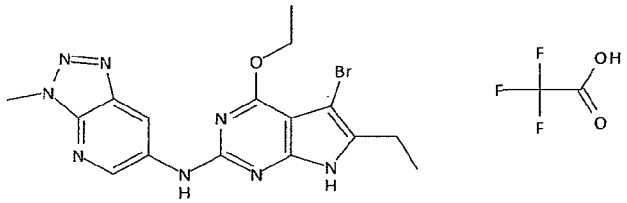
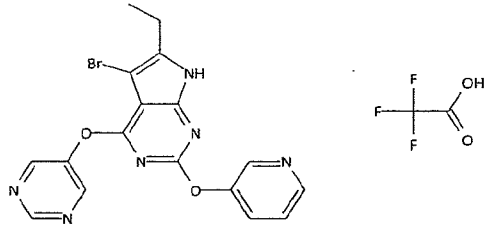
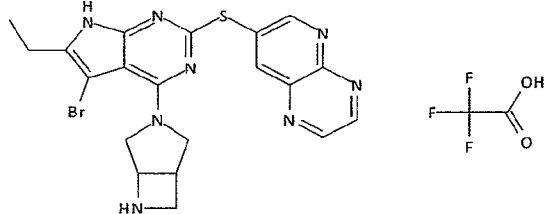
Rx ID	CHEMISTRY
700,423	 Chemistry 55
700,433	 Chemistry 56
700,443	 Chemistry 57
700,450	 Chemistry 58
700,451	 Chemistry 59

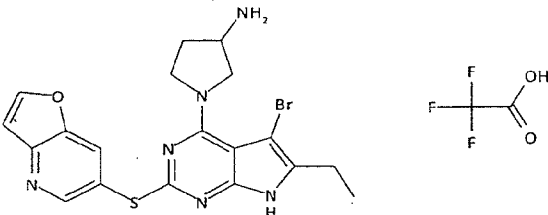
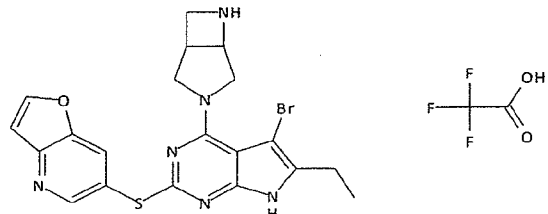
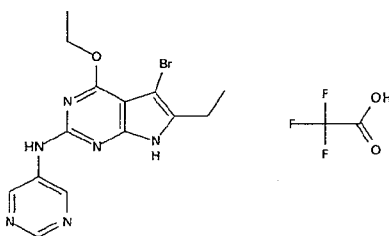
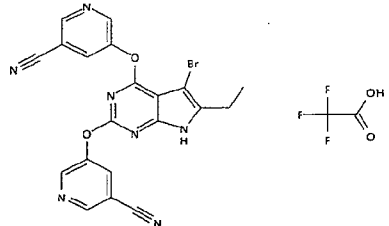
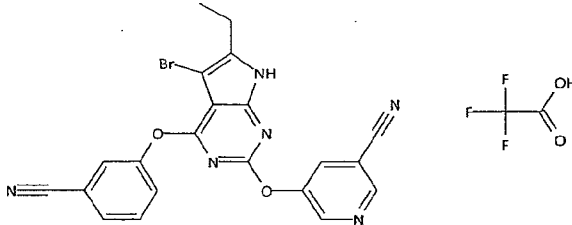
Rx ID	CHEMISTRY
700,452	 Chemistry 60
700,467	 Chemistry 61
700,468	 Chemistry 62
700,469	 Chemistry 63
700,470	 Chemistry 64

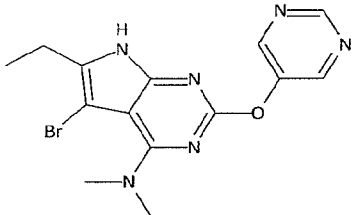
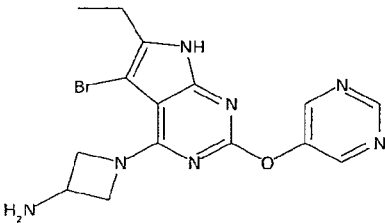
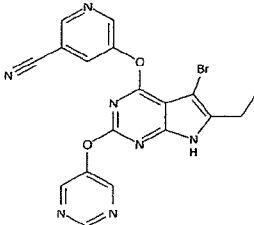
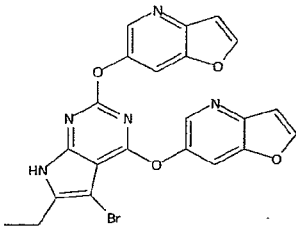
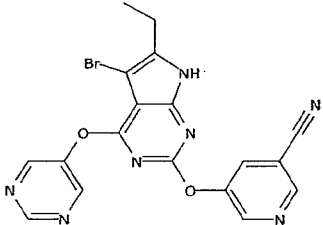
Rx ID	CHEMISTRY
700,471	 Chemistry 65
700,475	 Chemistry 66
700,476	 Chemistry 67
700,481	 Chemistry 68
700,482	 Chemistry 69

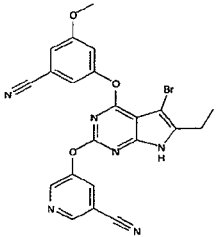
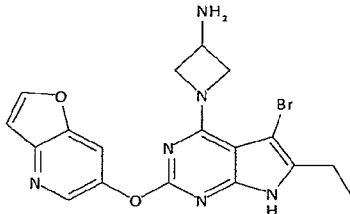
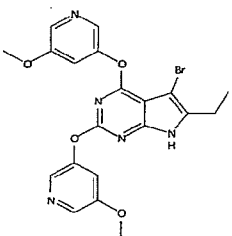
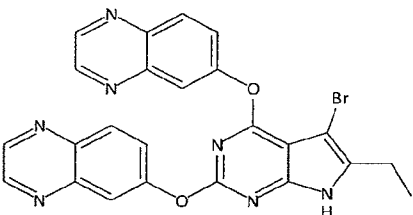
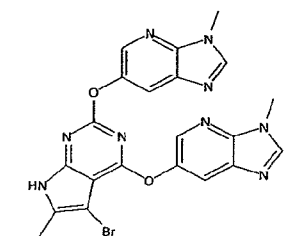
Rx ID	CHEMISTRY
700,483	 Chemistry 70
700,484	 Chemistry 71
700,485	 Chemistry 72
700,498	 Chemistry 73
700,496	 Chemistry 74

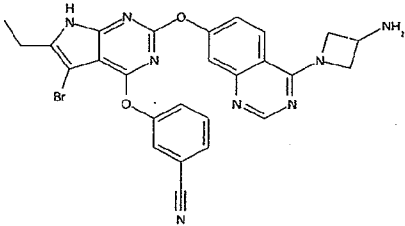
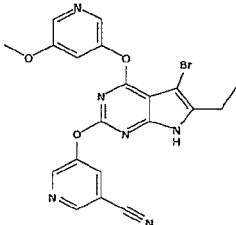
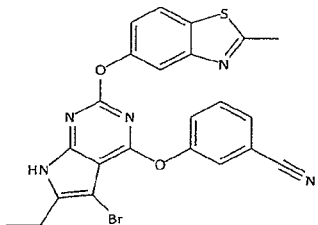
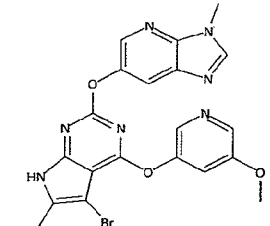
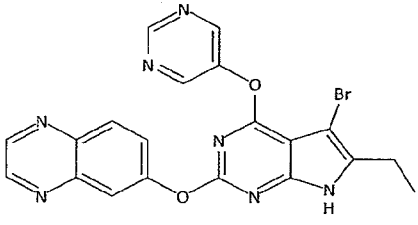
Rx ID	CHEMISTRY
700,535	 Chemistry 75
700,545	 Chemistry 76
700,552	 Chemistry 77
700,572	 Chemistry 78
700,591	 Chemistry 79

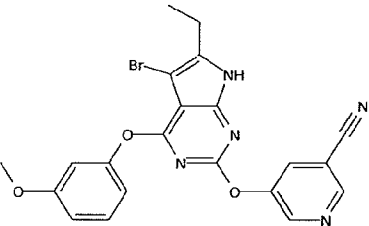
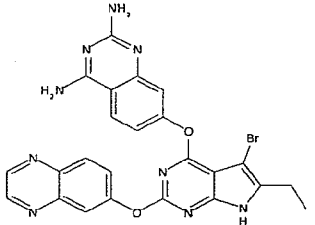
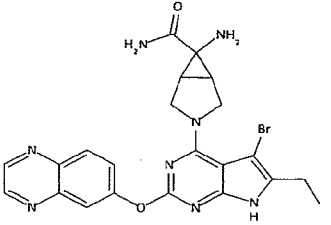
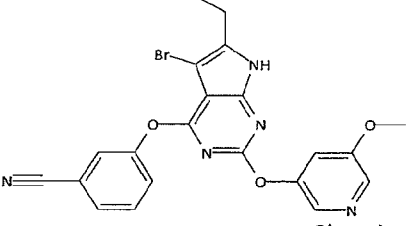
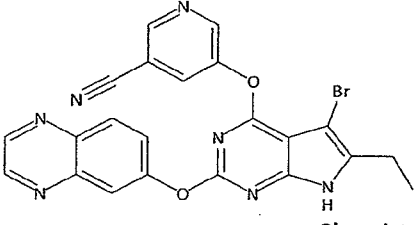
Rx ID	CHEMISTRY
700,598	 Chemistry 80
700,599	 Chemistry 81
700,600	 Chemistry 82
700,621	 Chemistry 83
700,673	 Chemistry 84

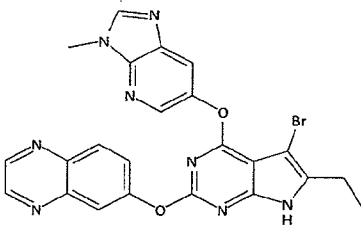
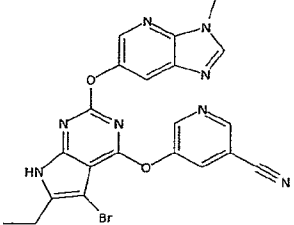
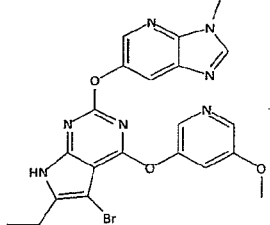
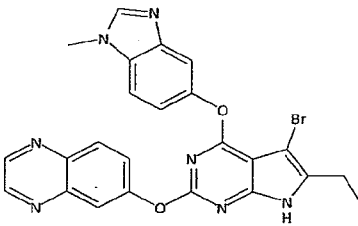
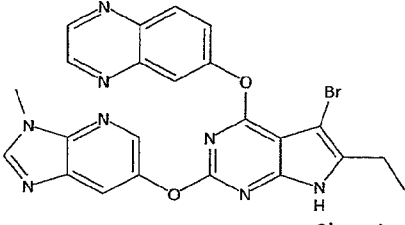
Rx ID	CHEMISTRY
700,679	 Chemistry 85
700,680	 Chemistry 86
700,701	 Chemistry 87
700,724	 Chemistry 88
700,793	 Chemistry 89

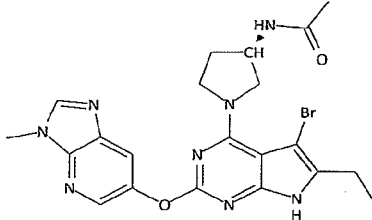
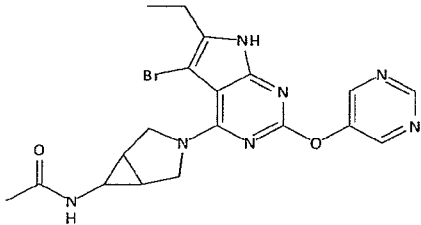
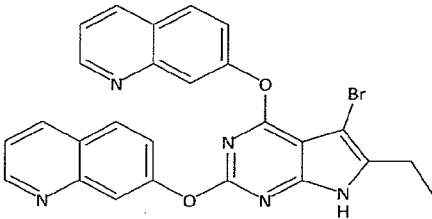
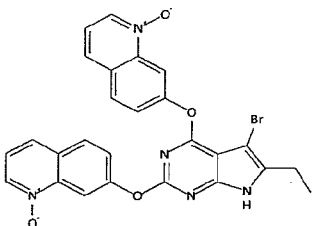
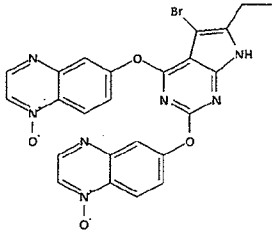
Rx ID	CHEMISTRY
700,866	 Chemistry 90
700,877	 Chemistry 91
700,878	 Chemistry 92
700,883	 Chemistry 93
700,899	 Chemistry 94

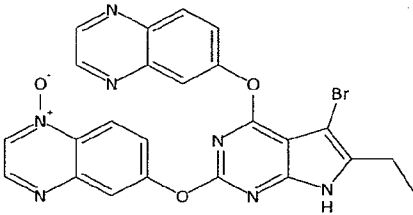
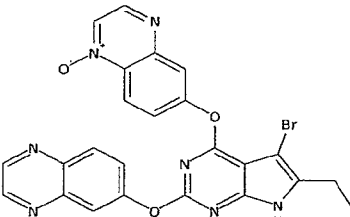
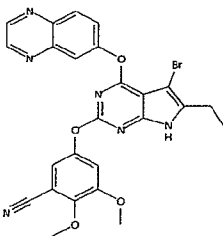
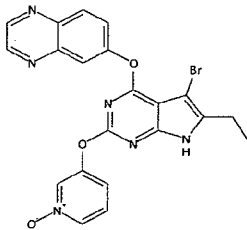
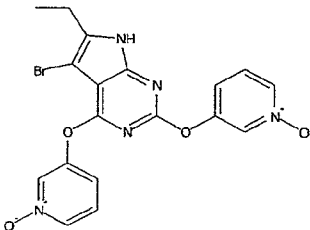
Rx ID	CHEMISTRY
700,933	 Chemistry 95
700,935	 Chemistry 96
700,937	 Chemistry 97
700,938	 Chemistry 98
700,939	 Chemistry 99

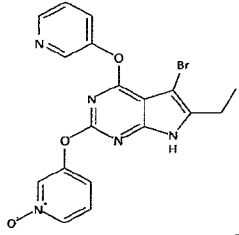
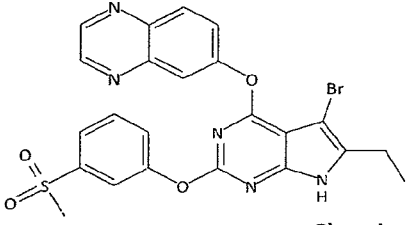
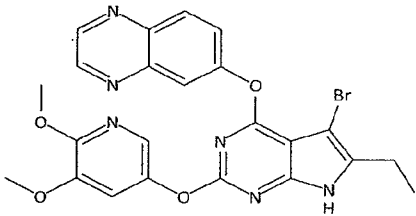
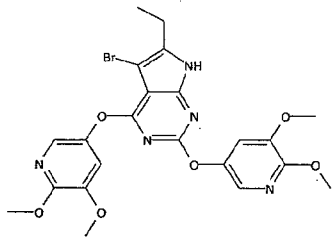
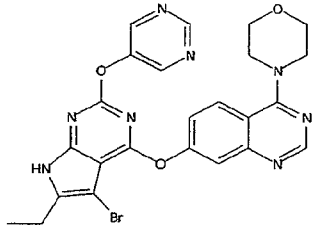
Rx ID	CHEMISTRY
700,944	 Chemistry 100
700,945	 Chemistry 101
700,949	 Chemistry 102
700,964	 Chemistry 103
700,965	 Chemistry 104

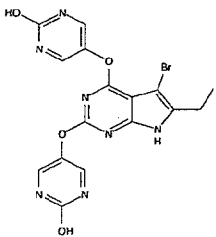
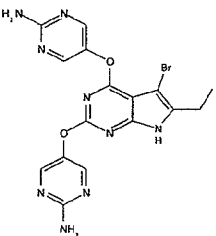
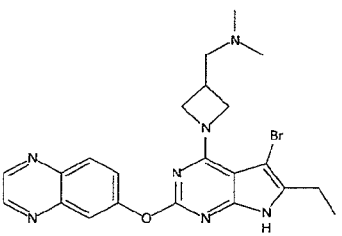
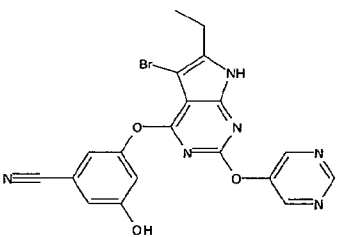
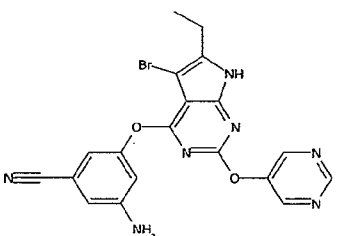
Rx ID	CHEMISTRY
700,966	 Chemistry 105
700,979	 Chemistry 106
700,980	 Chemistry 107
700,982	 Chemistry 108
700,987	 Chemistry 109

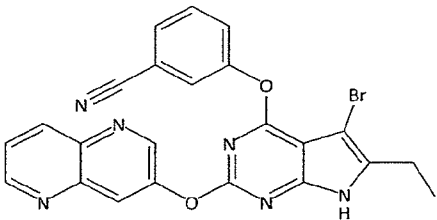
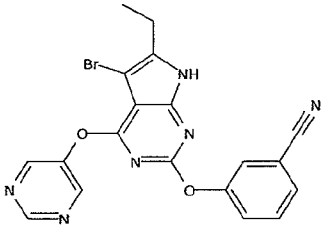
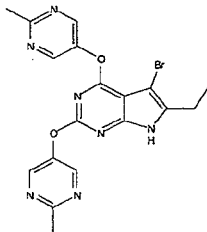
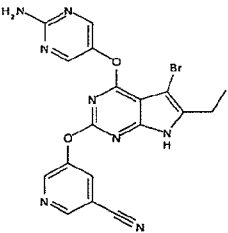
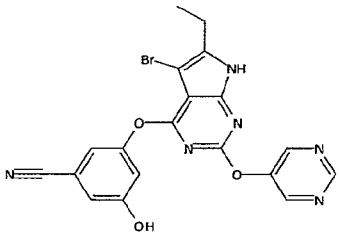
Rx ID	CHEMISTRY
700,988	 Chemistry 110
700,996	 Chemistry 111
700,997	 Chemistry 112
700,998	 Chemistry 113
701,030	 Chemistry 114

Rx ID	CHEMISTRY
701,032	 Chemistry 115
701,052	 Chemistry 116
701,054	 Chemistry 117
701,056	 Chemistry 118
701,058	 Chemistry 119

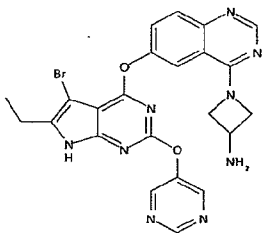
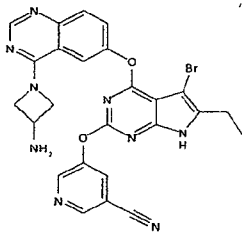
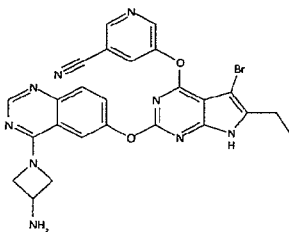
Rx ID	CHEMISTRY
701,059	 Chemistry 120
701,060	 Chemistry 121
701,081	 Chemistry 122
701,091	 Chemistry 123
701,092	 Chemistry 124

Rx ID	CHEMISTRY
701,093	 Chemistry 125
701,095	 Chemistry 126
701,096	 Chemistry 127
701,097	 Chemistry 128
701,104	 Chemistry 129

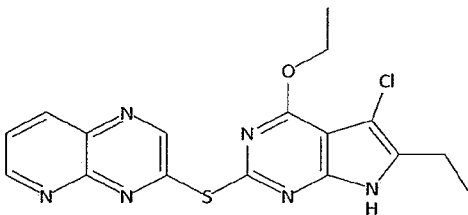
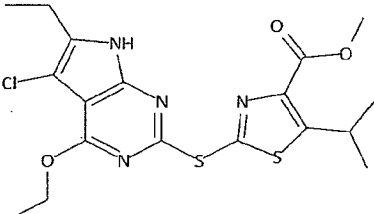
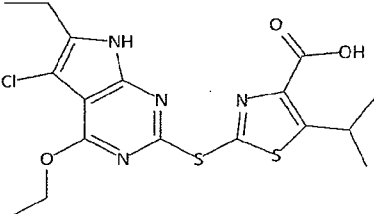
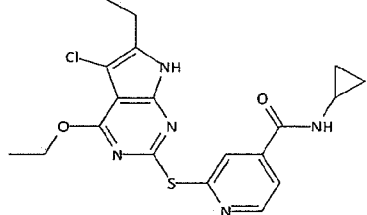
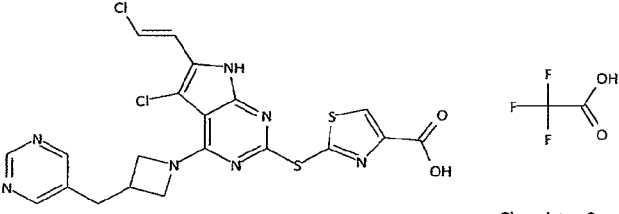
Rx ID	CHEMISTRY
701,105	 Chemistry 130
701,106	 Chemistry 131
701,114	 Chemistry 132
701,249	 Chemistry 133
701,250	 Chemistry 134

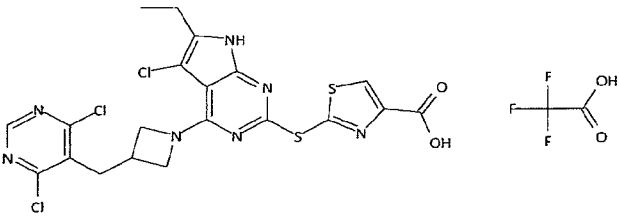
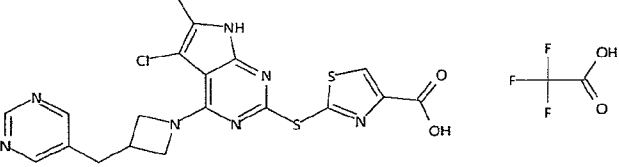
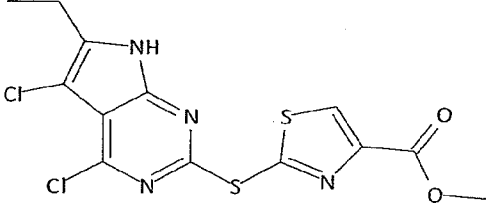
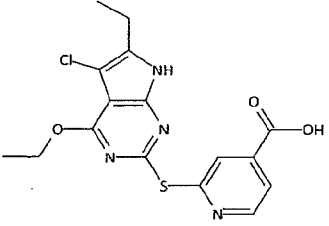
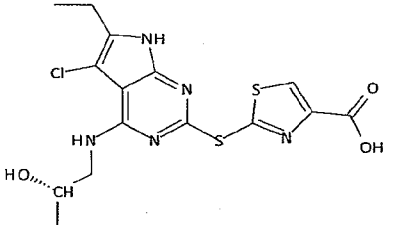
Rx ID	CHEMISTRY
701,252	 Chemistry 135
701,253	 Chemistry 136
701,254	 Chemistry 137
701,255	 Chemistry 138
701249-2	 Chemistry 139

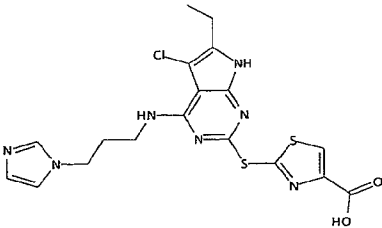
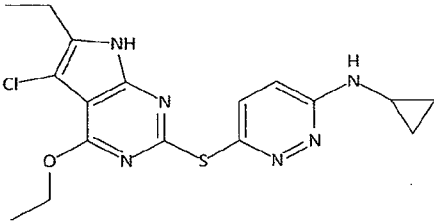
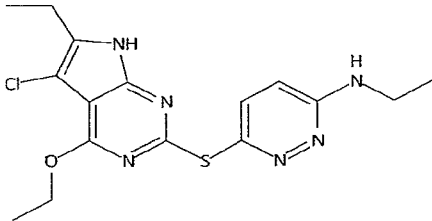
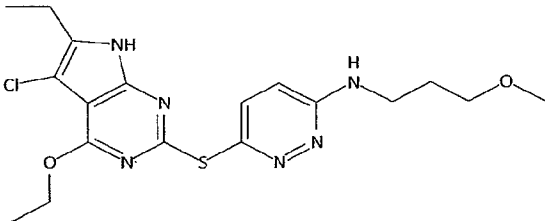
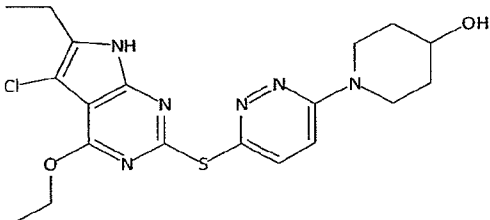
Rx ID	CHEMISTRY
701,267	 Chemistry 140
701,268	 Chemistry 141
701,273	 Chemistry 142
701,287	 Chemistry 143
701,288	 Chemistry 144

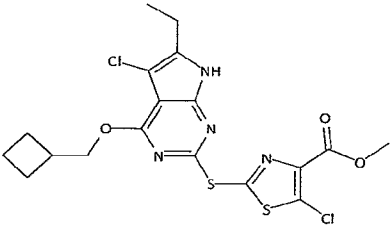
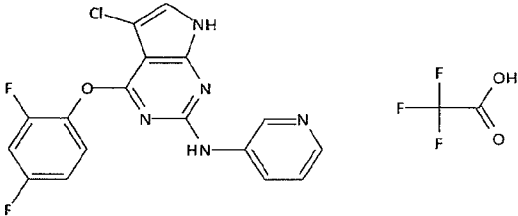
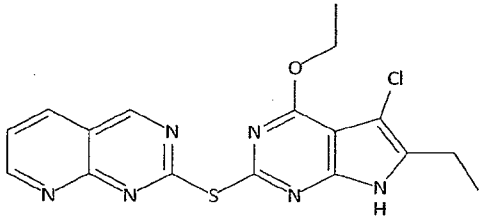
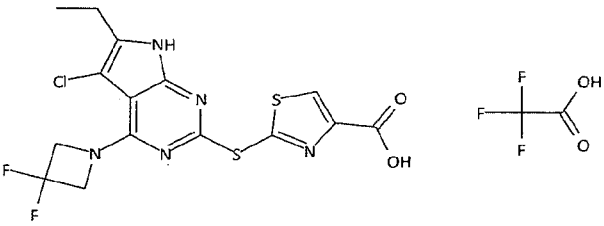
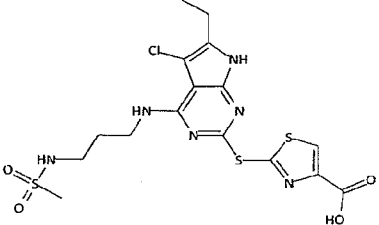
Rx ID	CHEMISTRY
701,297	 Chemistry 145
701,298	 Chemistry 146
701,299	 Chemistry 147

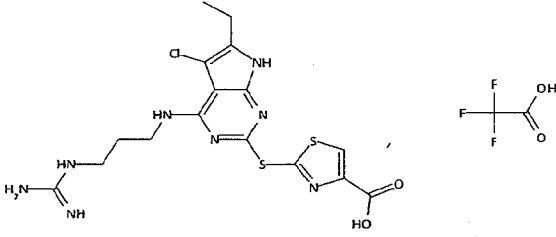
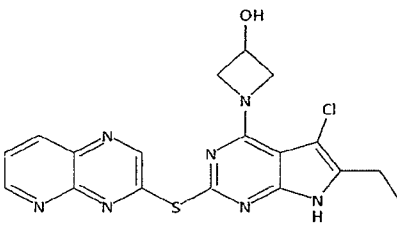
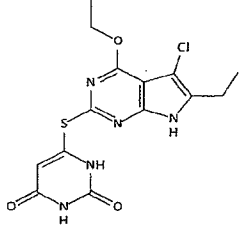
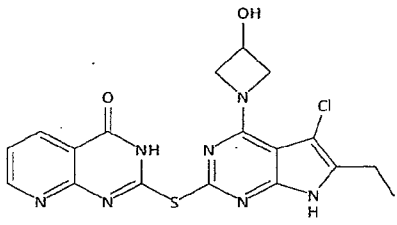
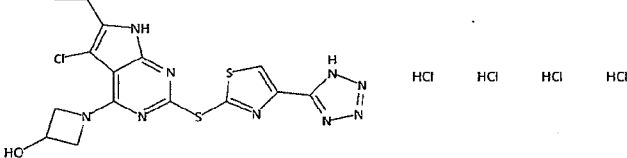
Rx ID	CHEMISTRY
700,339	 Chemistry 0
700,340	 Chemistry 1
700,268	 Chemistry 2
700,273	 Chemistry 3
700,274	 Chemistry 4

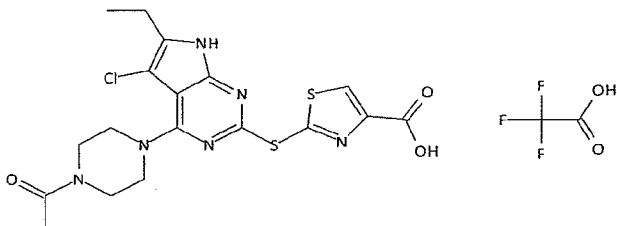
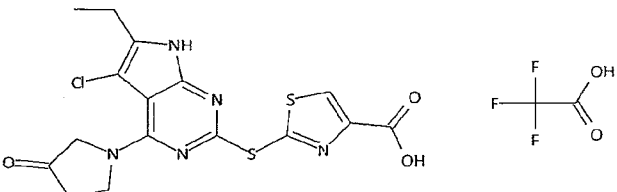
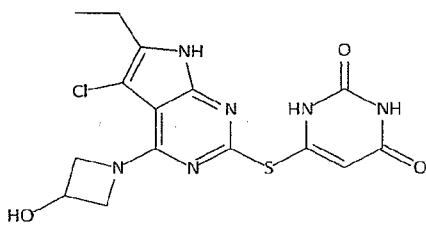
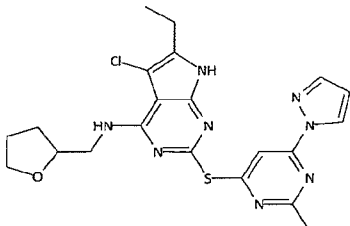
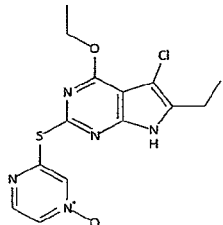
Rx ID	CHEMISTRY
700,298	 Chemistry 5
700,302	 Chemistry 6
700,304	 Chemistry 7
700,306	 Chemistry 8
700,316	 Chemistry 9

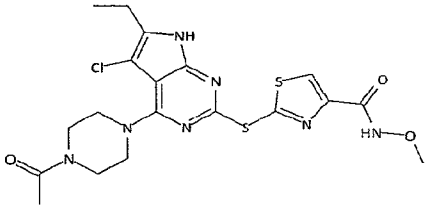
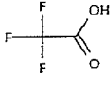
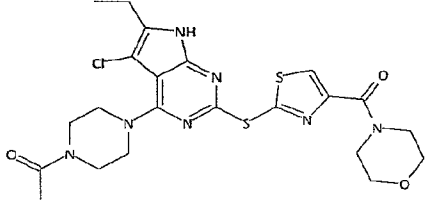
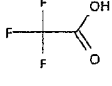
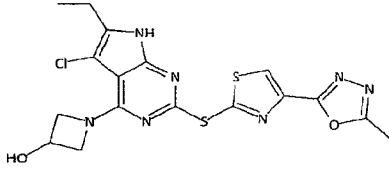
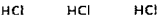
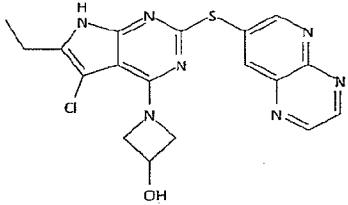
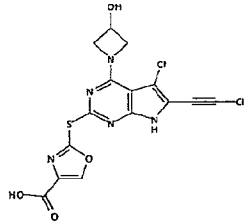
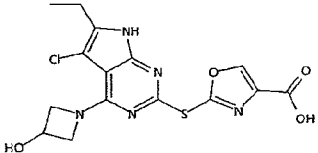
Rx ID	CHEMISTRY
700,317	 Chemistry 10
700,318	 Chemistry 11
700,320	 Chemistry 12
700,321	 Chemistry 13
700,322	 Chemistry 14

Rx ID	CHEMISTRY
700,323	 Chemistry 15
700,324	 Chemistry 16
700,325	 Chemistry 17
700,326	 Chemistry 18
700,327	 Chemistry 19

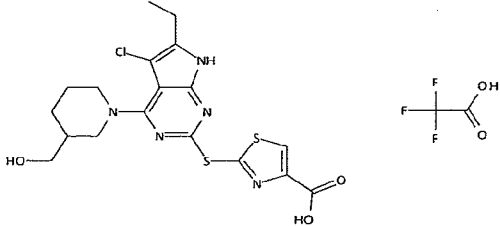
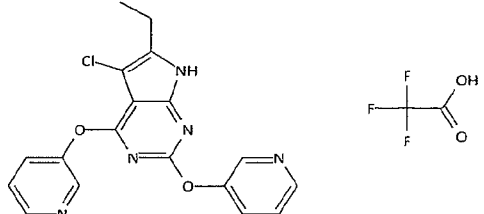
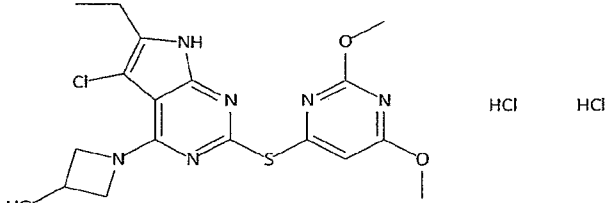
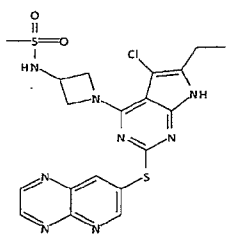
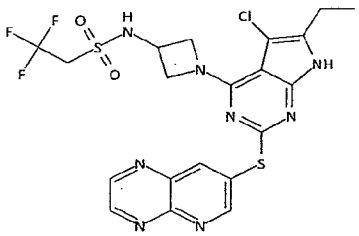
Rx ID	CHEMISTRY
700,328	 Chemistry 20
700,330	 Chemistry 21
700,341	 Chemistry 22
700,338	 Chemistry 23
700,342	 Chemistry 24

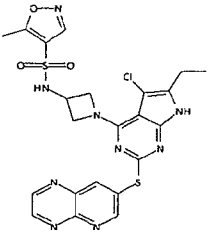
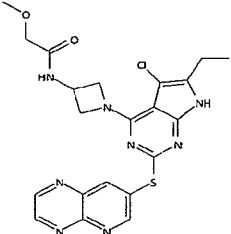
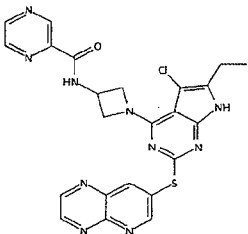
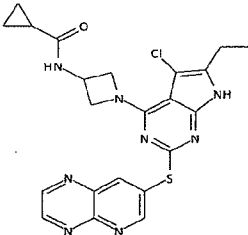
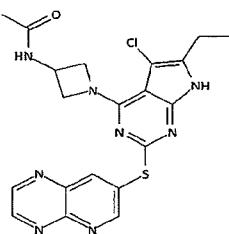
Rx ID	CHEMISTRY
700,343	 Chemistry 25
700,345	 Chemistry 26
700,347	 Chemistry 27
700,353	 Chemistry 28
700,355	 Chemistry 29

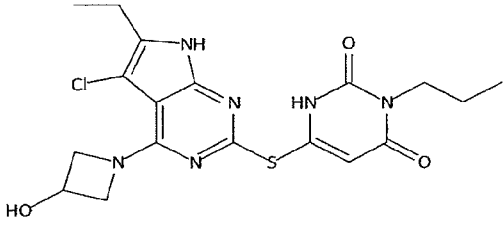
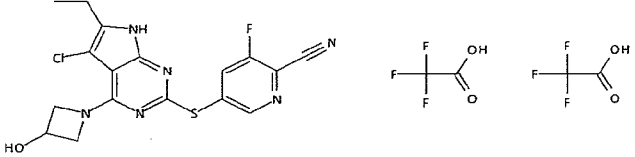
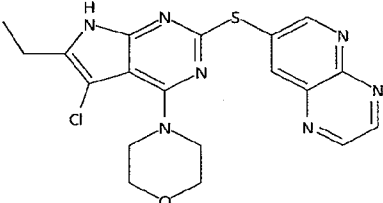
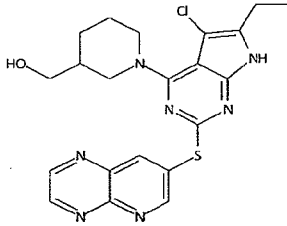
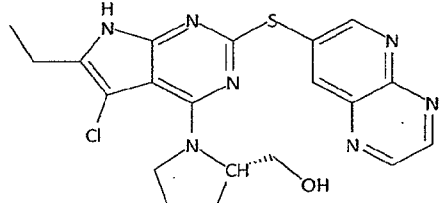
Rx ID	CHEMISTRY
700,356	 Chemistry 30
700,357	 Chemistry 31
700,359	 Chemistry 32
700,373	 Chemistry 33
700,361	 Chemistry 34

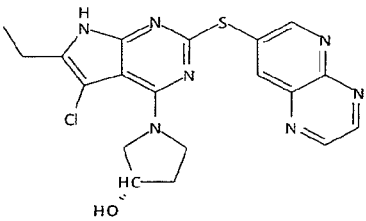
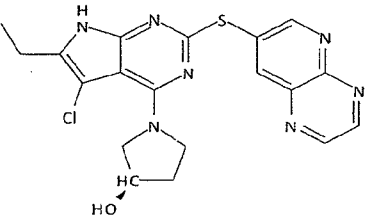
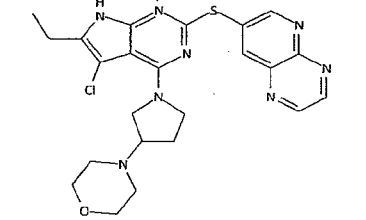
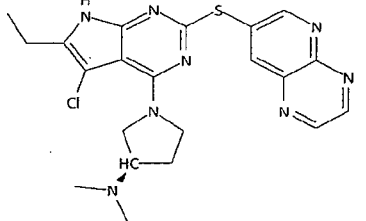
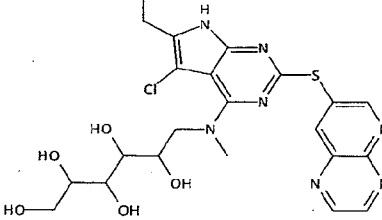
Rx ID	CHEMISTRY
700,364	 
700,365	 
700,387	 
700,393	
700,394	  
700,395	  

Rx ID	CHEMISTRY
700,396	 Chemistry 41
700,397	 Chemistry 42
700,398	 Chemistry 43
700,406	 Chemistry 44
700,407	 Chemistry 45

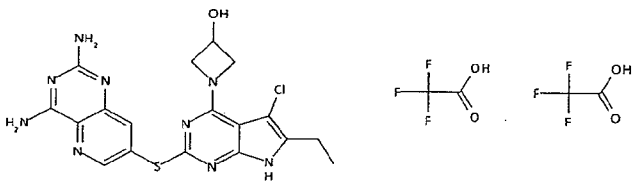
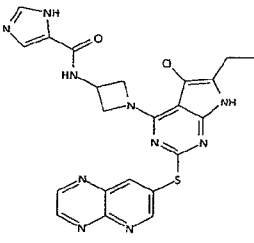
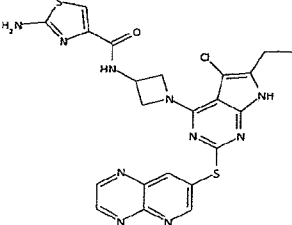
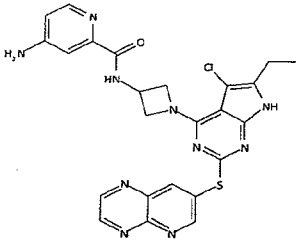
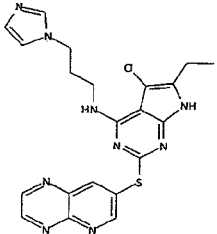
Rx ID	CHEMISTRY
700,408	 Chemistry 46
700,410	 Chemistry 47
700,411	 Chemistry 48
700,435	 Chemistry 49
700,436	 Chemistry 50

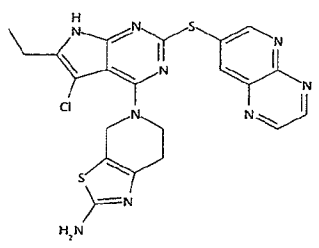
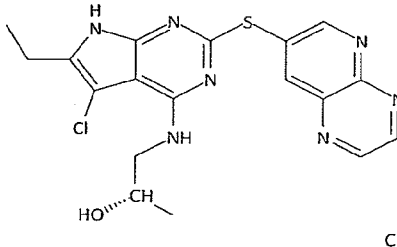
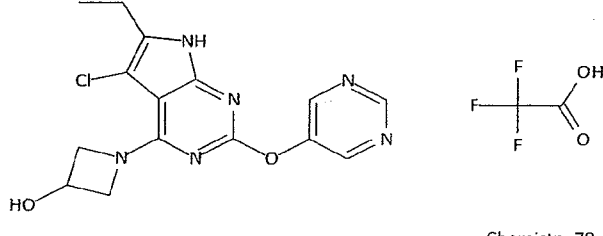
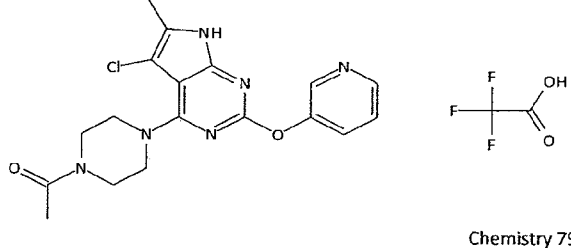
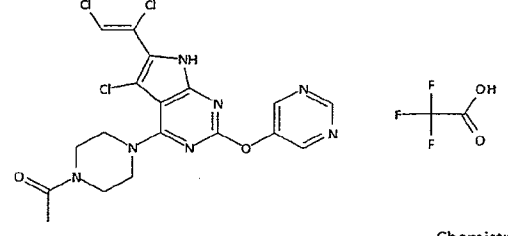
Rx ID	CHEMISTRY
700,437	 Chemistry 51
700,438	 Chemistry 52
700,439	 Chemistry 53
700,440	 Chemistry 54
700,441	 Chemistry 55

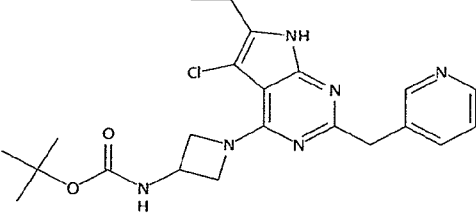
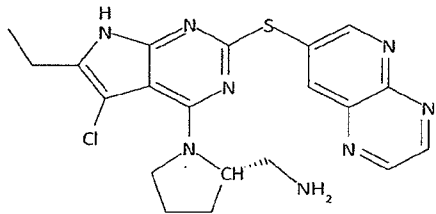
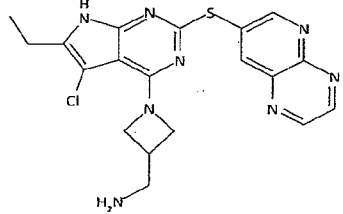
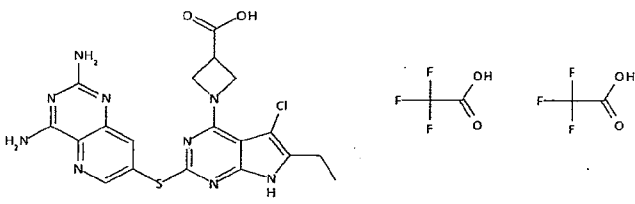
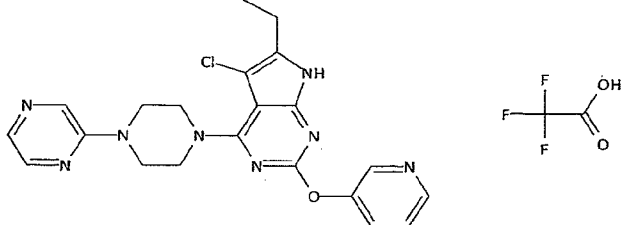
Rx ID	CHEMISTRY
700,418	 Chemistry 56
700,422	 Chemistry 57
700,424	 Chemistry 58
700,425	 Chemistry 59
700,426	 Chemistry 60

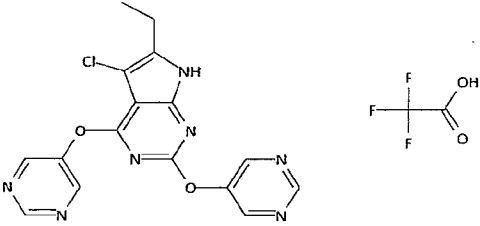
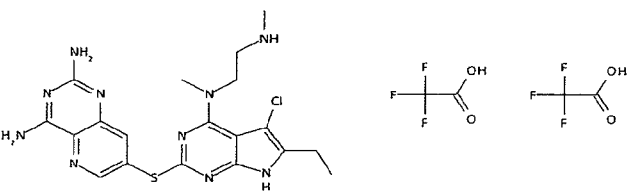
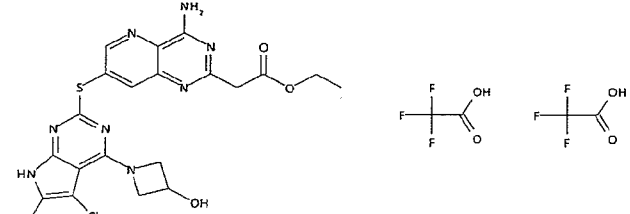
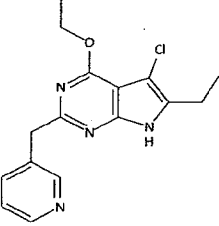
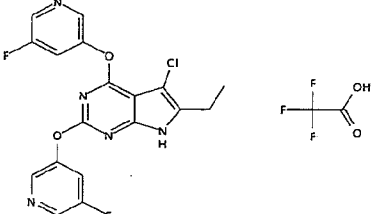
Rx ID	CHEMISTRY
700,427	 Chemistry 61
700,428	 Chemistry 62
700,429	 Chemistry 63
700,430	 Chemistry 64
700,431	 Chemistry 65

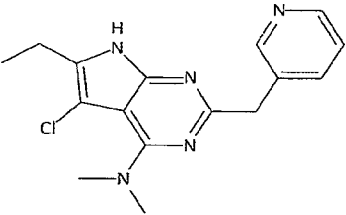
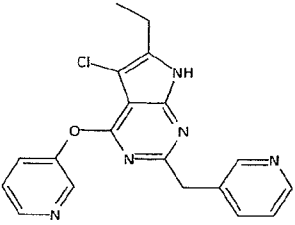
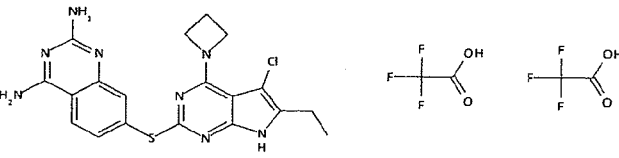
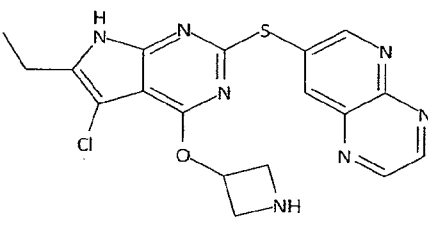
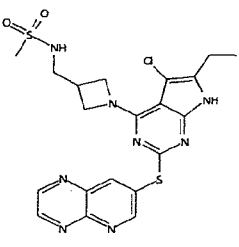
Rx ID	CHEMISTRY
700,432	 Chemistry 66
700,434	 Chemistry 67
700,444	 Chemistry 68
700,445	 Chemistry 69
101,566	 Chemistry 70

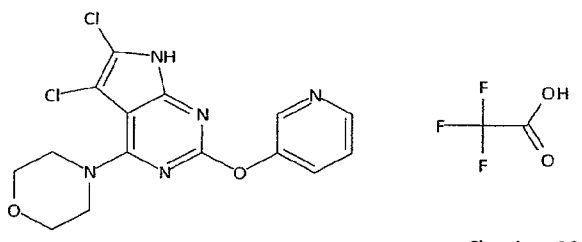
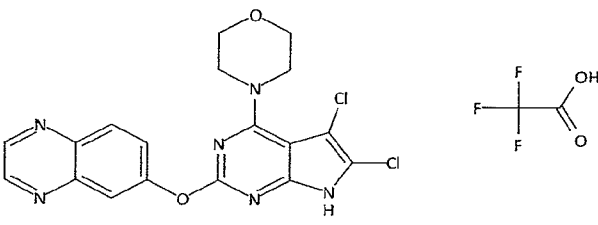
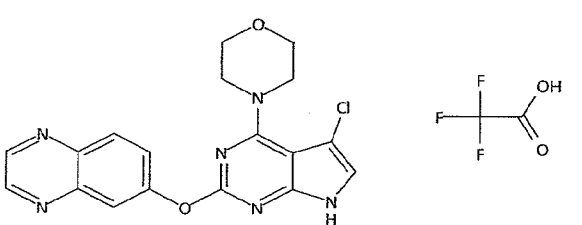
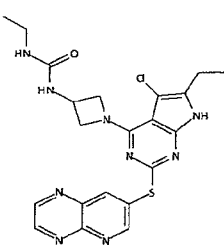
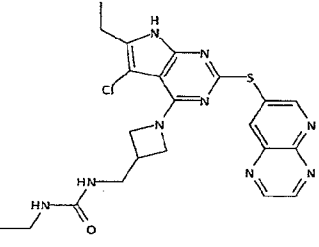
Rx ID	CHEMISTRY
700,448	 Chemistry 71
700,449	 Chemistry 72
700,453	 Chemistry 73
700,454	 Chemistry 74
700,455	 Chemistry 75

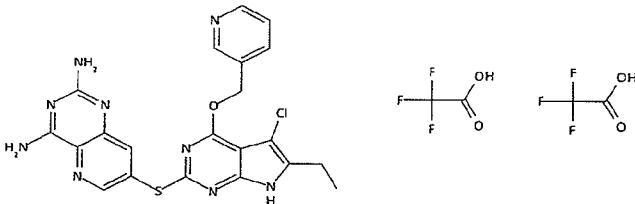
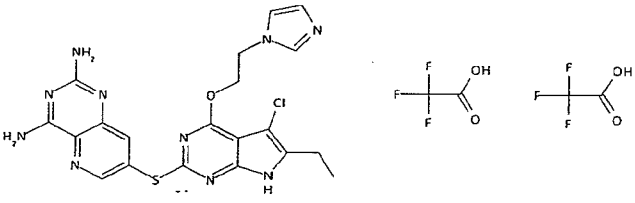
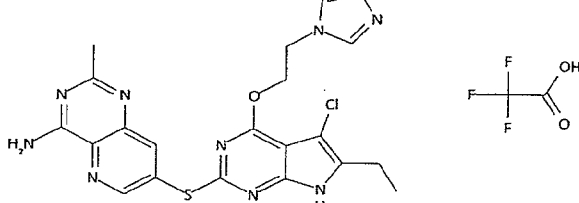
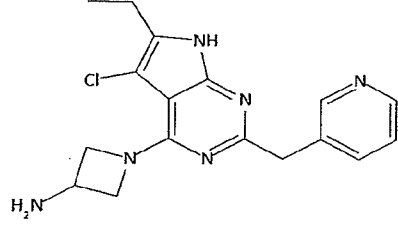
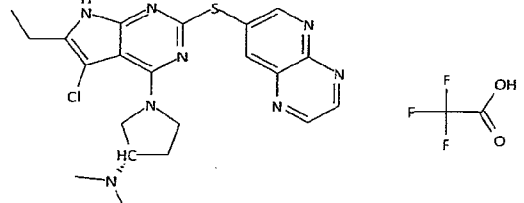
Rx ID	CHEMISTRY
700,456	 Chemistry 76
700,457	 Chemistry 77
700,458	 Chemistry 78
700,459	 Chemistry 79
700,460	 Chemistry 80

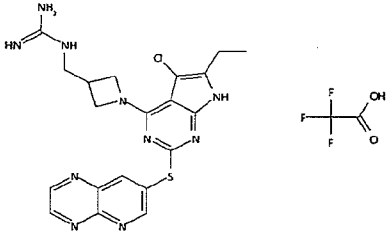
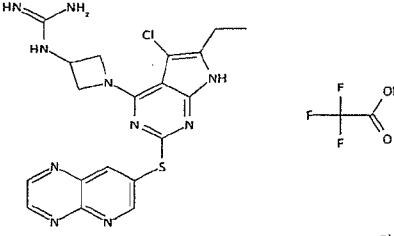
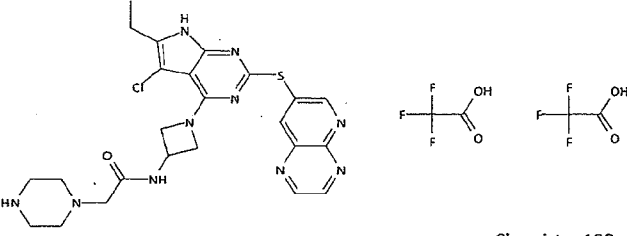
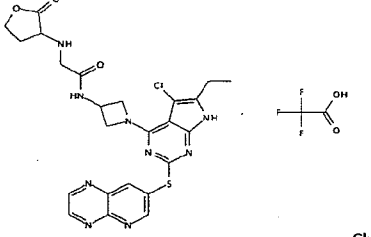
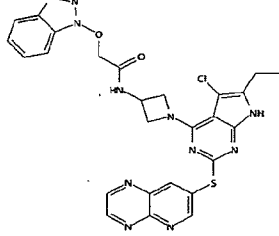
Rx ID	CHEMISTRY
700,461	 Chemistry 81
700,462	 Chemistry 82
700,463	 Chemistry 83
700,464	 Chemistry 84
700,465	 Chemistry 85

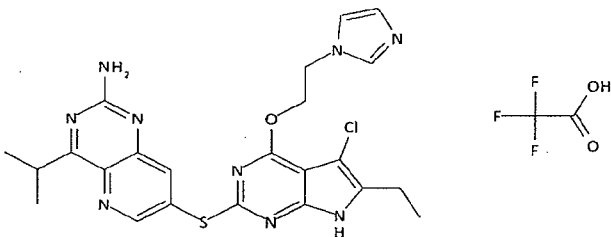
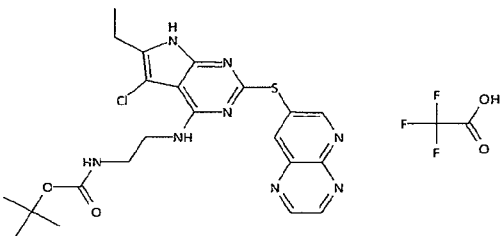
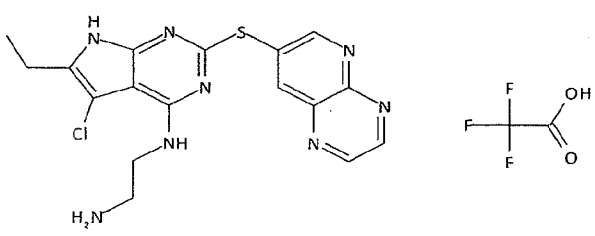
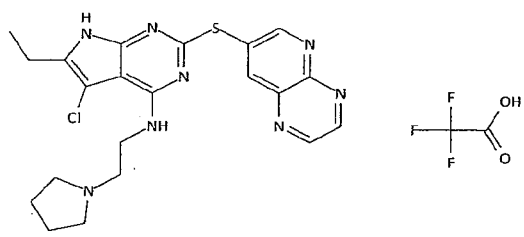
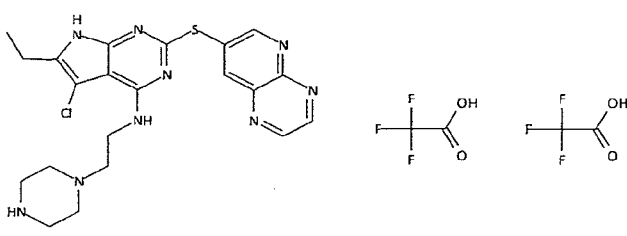
Rx ID	CHEMISTRY
700,466	 Chemistry 86
700,472	 Chemistry 87
700,473	 Chemistry 88
700,474	 Chemistry 89
700,477	 Chemistry 90

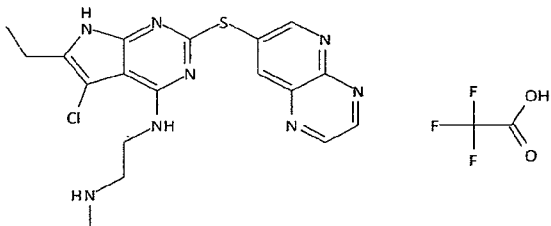
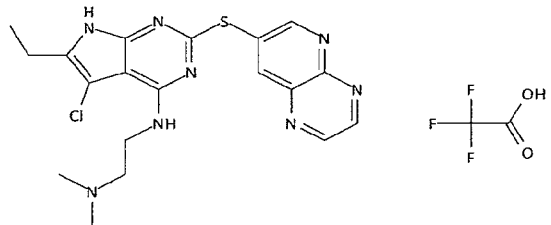
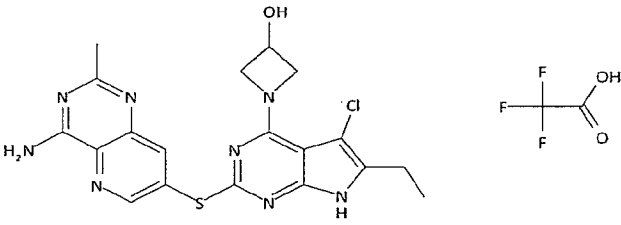
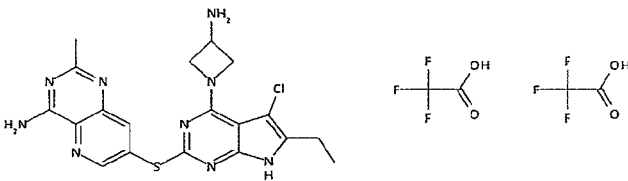
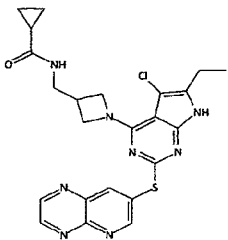
Rx ID	CHEMISTRY
700,478	 Chemistry 91
700,479	 Chemistry 92
700,480	 Chemistry 93
700,486	 Chemistry 94
700,487	 Chemistry 95

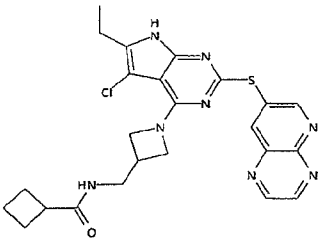
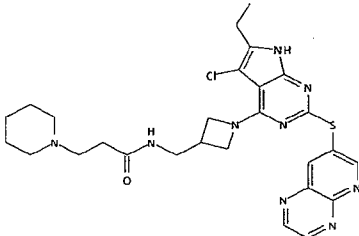
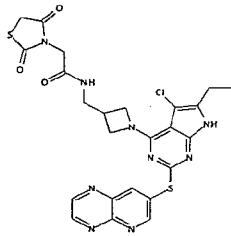
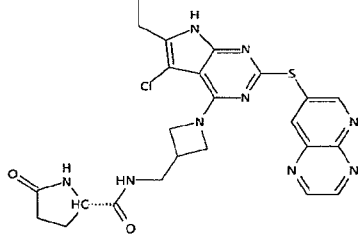
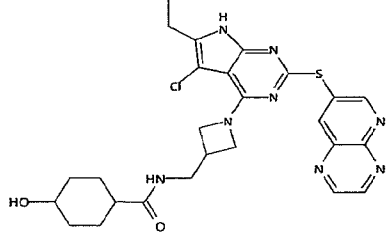
Rx ID	CHEMISTRY
700,499	 Chemistry 96
700,500	 Chemistry 97
700,501	 Chemistry 98
700,490	 Chemistry 99
700,491	 Chemistry 100

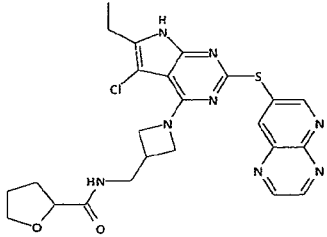
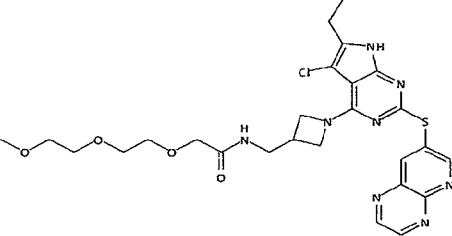
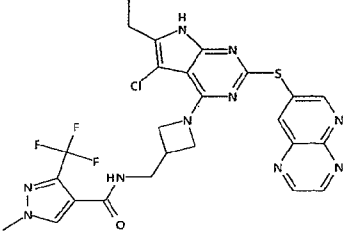
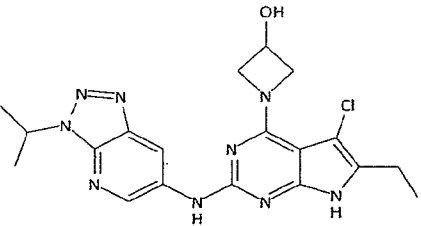
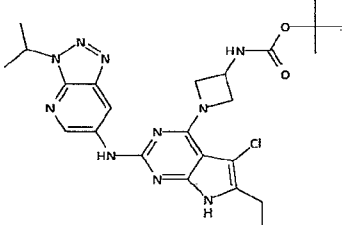
Rx ID	CHEMISTRY
700,492	 Chemistry 101
700,493	 Chemistry 102
700,494	 Chemistry 103
700,495	 Chemistry 104
700,497	 Chemistry 105

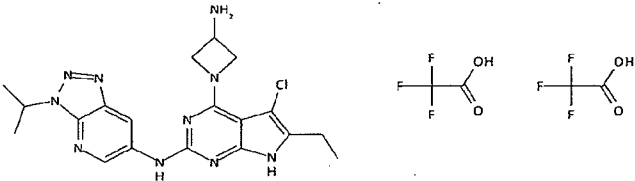
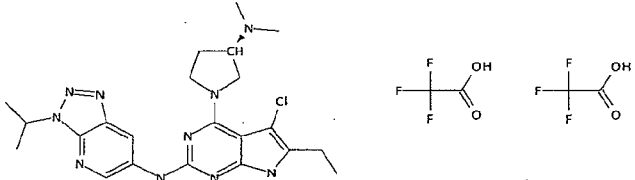
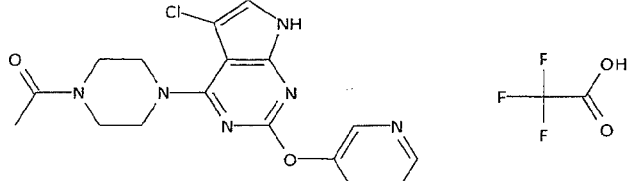
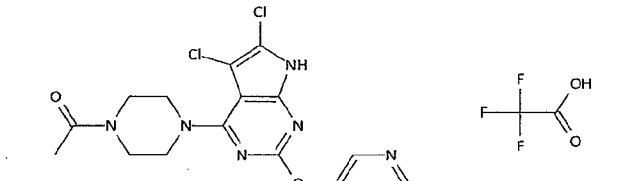
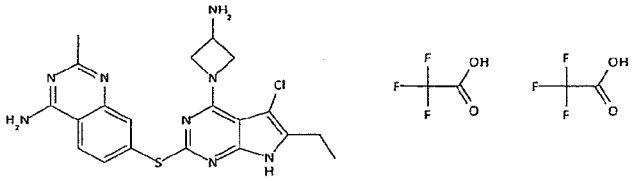
Rx ID	CHEMISTRY
700,502	 Chemistry 106
700,503	 Chemistry 107
700,504	 Chemistry 108
700,505	 Chemistry 109
700,506	 Chemistry 110

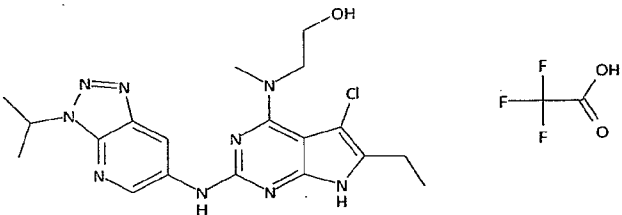
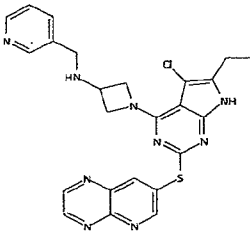
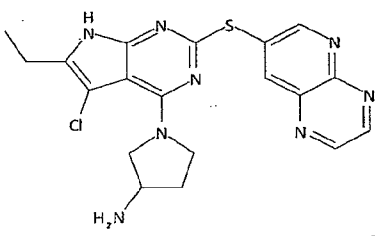
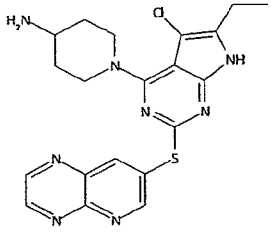
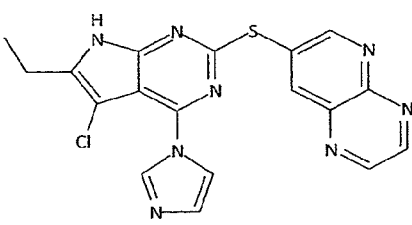
Rx ID	CHEMISTRY
700,507	 Chemistry 111
700,508	 Chemistry 112
700,509	 Chemistry 113
700,510	 Chemistry 114
700,511	 Chemistry 115

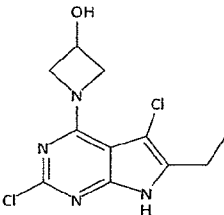
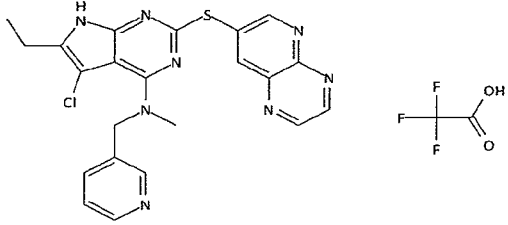
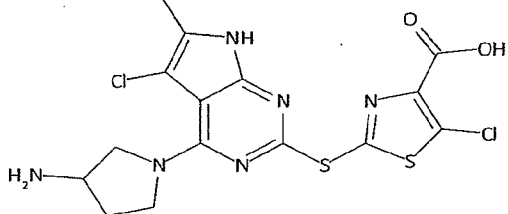
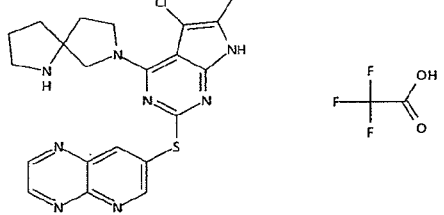
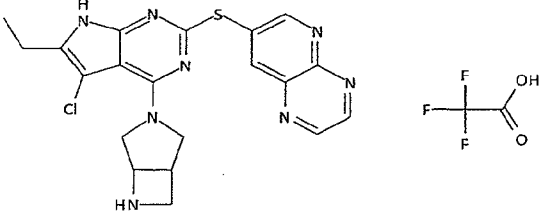
Rx ID	CHEMISTRY
700,512	 Chemistry 116
700,513	 Chemistry 117
700,514	 Chemistry 118
700,515	 Chemistry 119
700,516	 Chemistry 120

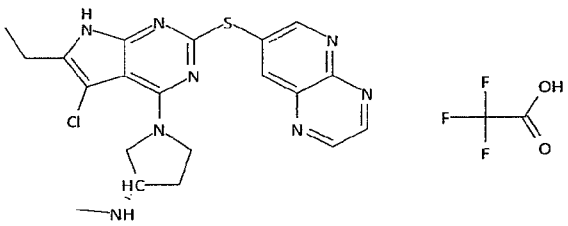
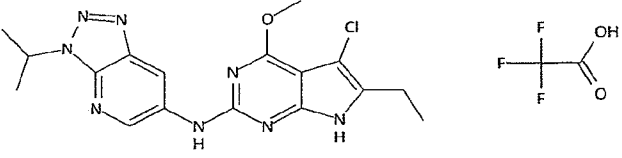
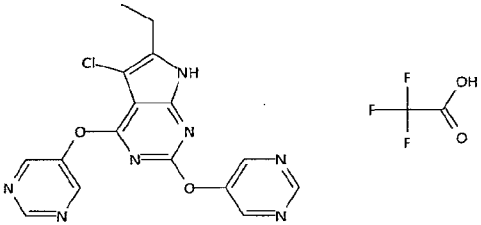
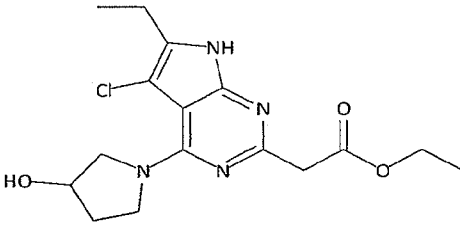
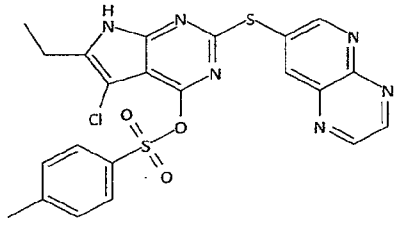
Rx ID	CHEMISTRY
700,517	 Chemistry 121
700,518	 Chemistry 122
700,519	 Chemistry 123
700,520	 Chemistry 124
700,521	 Chemistry 125

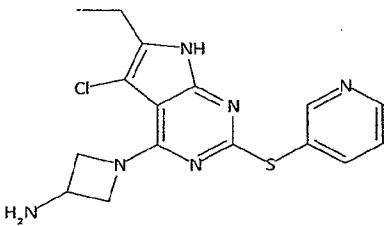
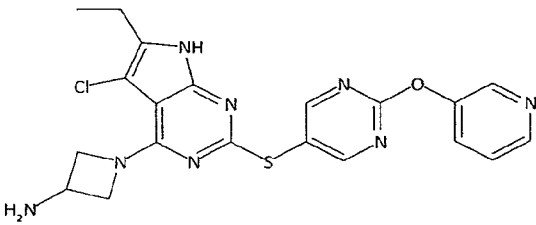
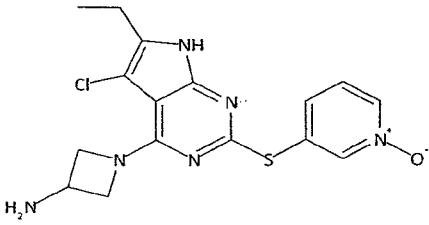
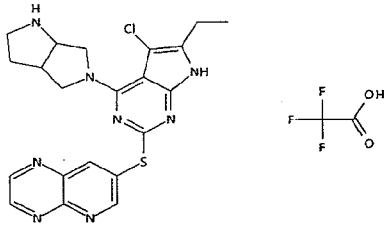
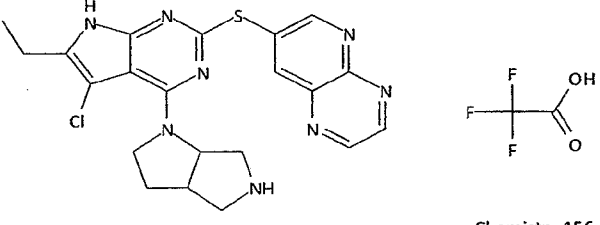
Rx ID	CHEMISTRY
700,522	 Chemistry 126
700,523	 Chemistry 127
700,524	 Chemistry 128
700,525	 Chemistry 129
700,526	 Chemistry 130

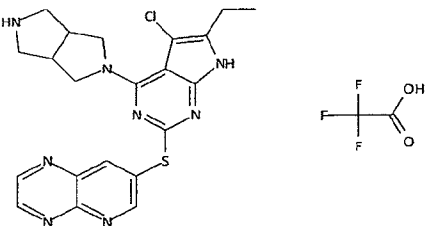
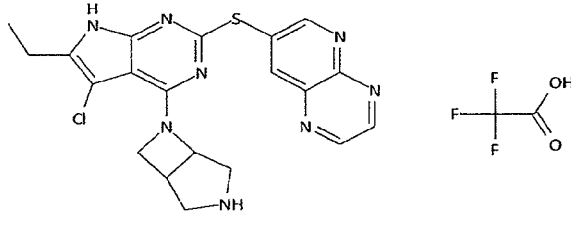
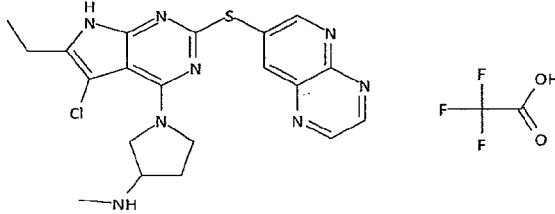
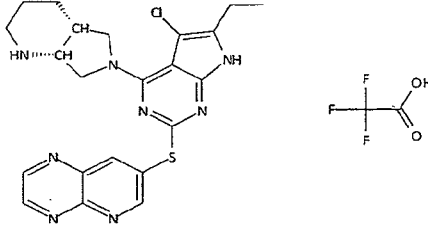
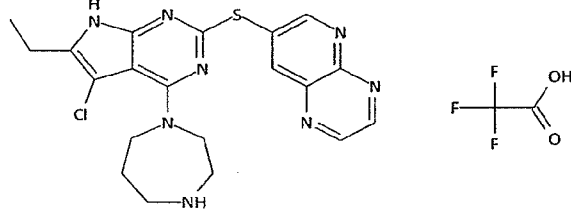
Rx ID	CHEMISTRY
700,527	 Chemistry 131
700,528	 Chemistry 132
700,529	 Chemistry 133
700,530	 Chemistry 134
700,531	 Chemistry 135

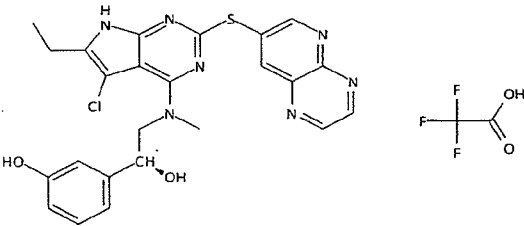
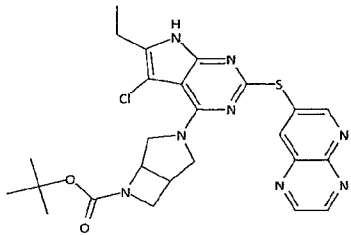
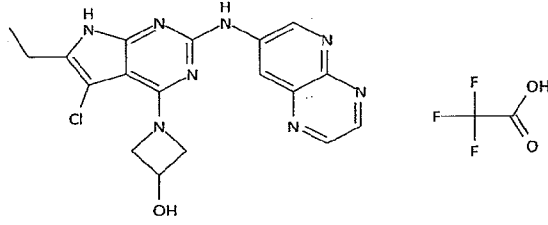
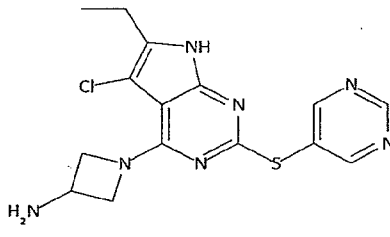
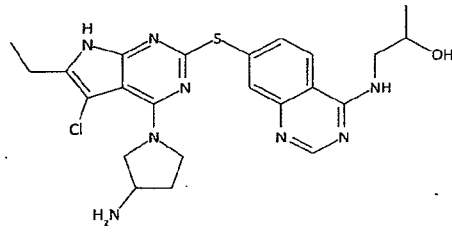
Rx ID	CHEMISTRY
700,534	 Chemistry 137
700,539	 Chemistry 138
700,540	 Chemistry 139
700,541	 Chemistry 140
700,542	 Chemistry 141

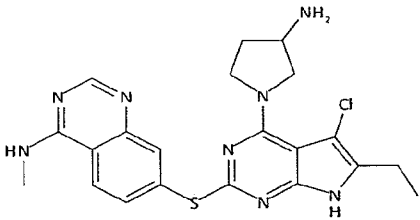
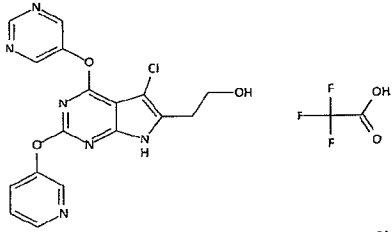
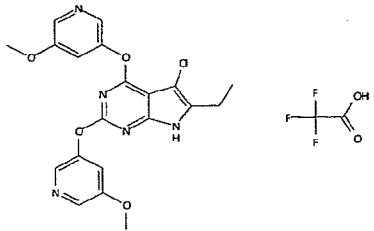
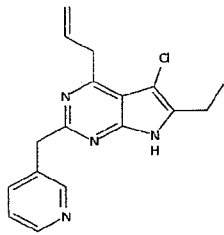
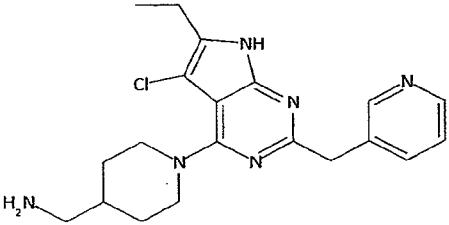
Rx ID	CHEMISTRY
700,543	 Chemistry 142
700,546	 Chemistry 143
700,559	 Chemistry 144
700,547	 Chemistry 145
700,548	 Chemistry 146

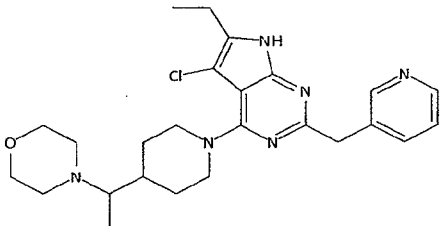
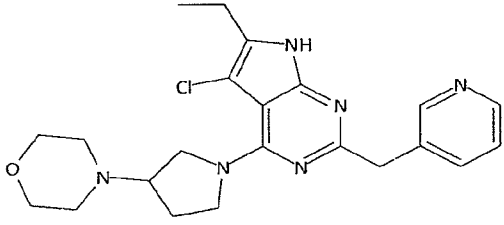
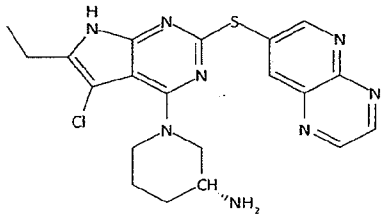
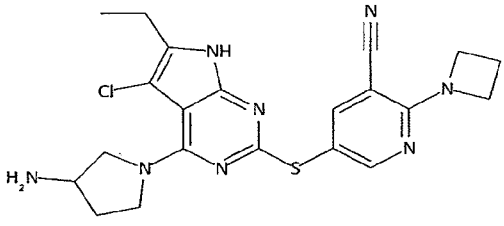
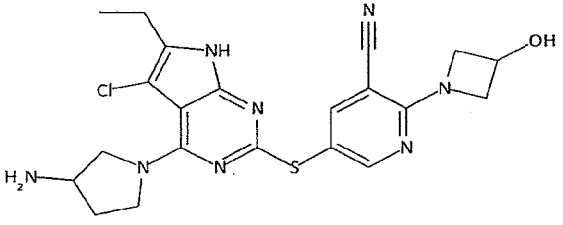
Rx ID	CHEMISTRY
700,549	 Chemistry 147
700,550	 Chemistry 148
700,551	 Chemistry 149
700,544	 Chemistry 150
700,558	 Chemistry 151

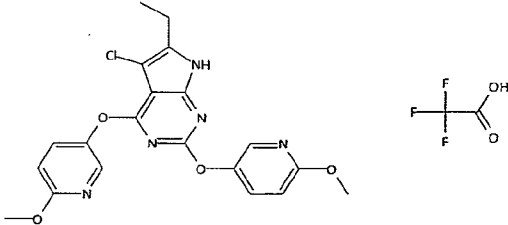
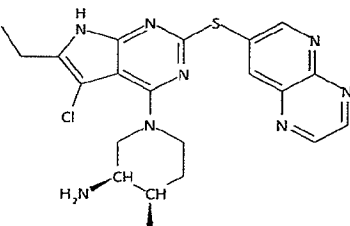
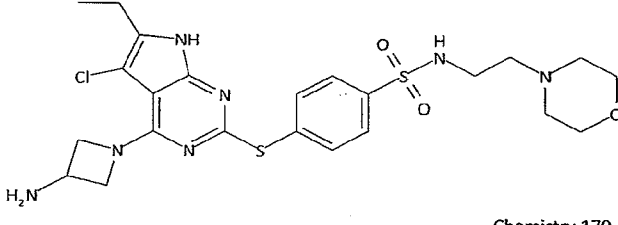
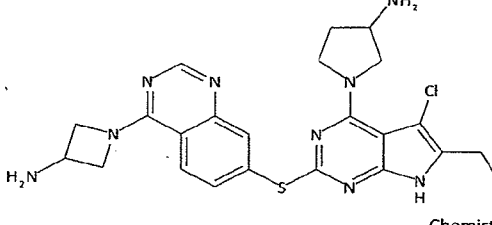
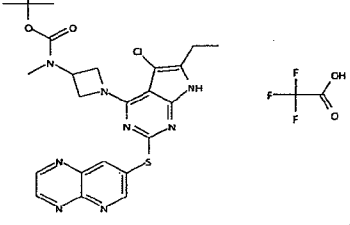
Rx ID	CHEMISTRY
700,560	 Chemistry 152
700,561	 Chemistry 153
700,562	 Chemistry 154
700,563	 Chemistry 155
700,564	 Chemistry 156

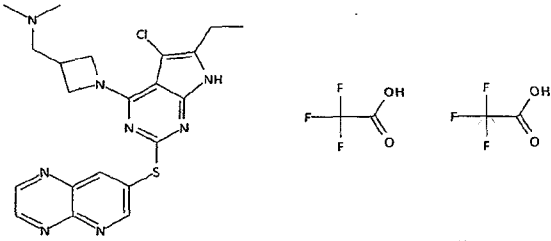
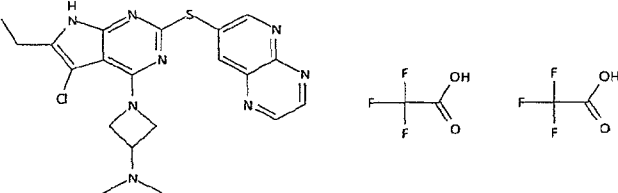
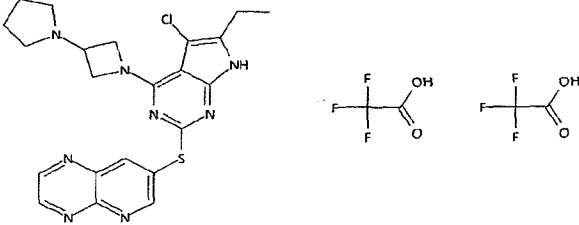
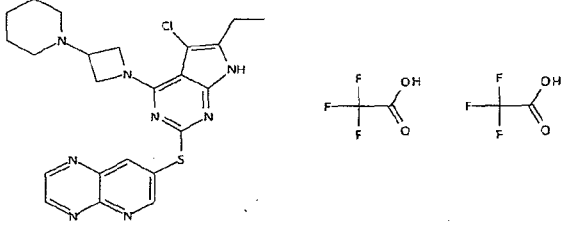
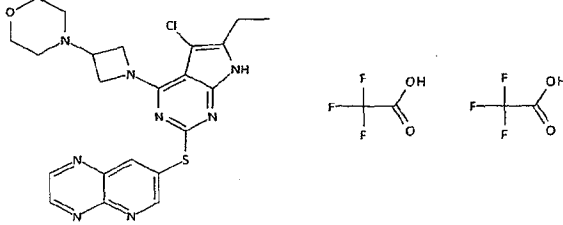
Rx ID	CHEMISTRY
700,565	 Chemistry 157
700,566	 Chemistry 158
700,567	 Chemistry 159
700,568	 Chemistry 160
700,569	 Chemistry 161

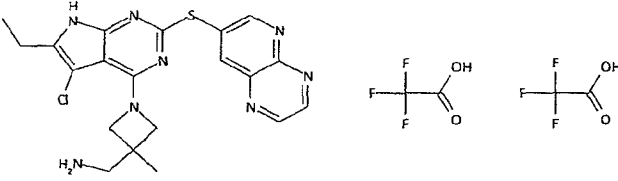
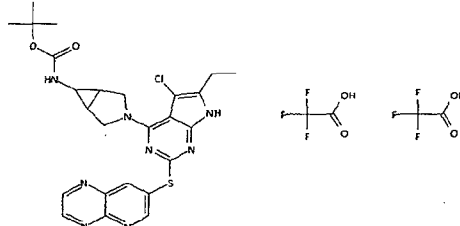
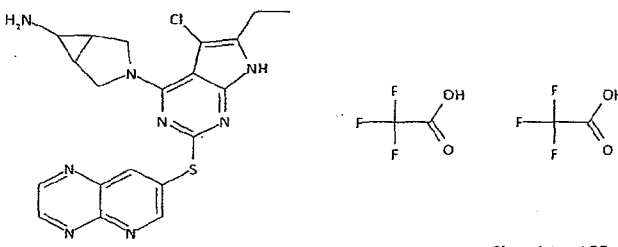
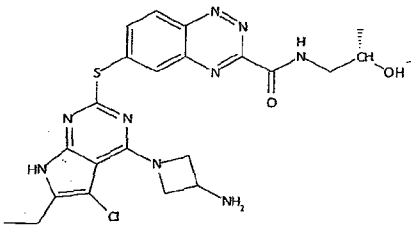
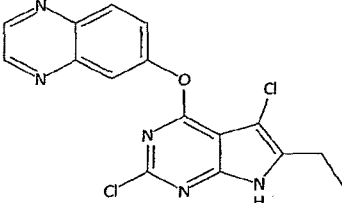
Rx ID	CHEMISTRY
700,570	 Chemistry 162
700,571	 Chemistry 163
700,573	 Chemistry 164
700,574	 Chemistry 165
700,575	 Chemistry 166

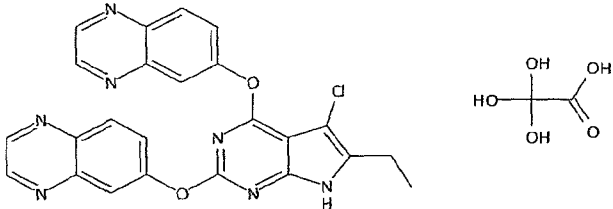
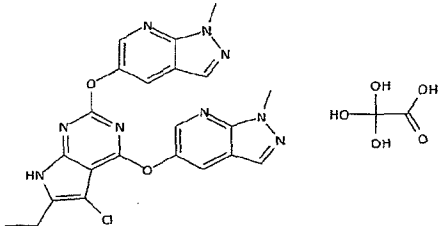
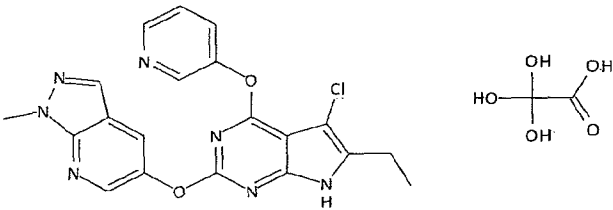
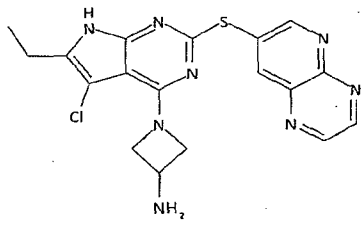
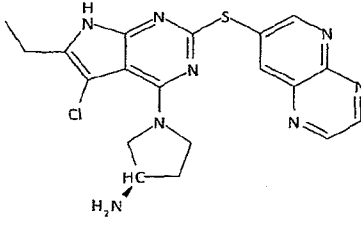
Rx ID	CHEMISTRY
700,576	 Chemistry 167
700,577	 Chemistry 168
700,578	 Chemistry 169
700,584	 Chemistry 170
700,585	 Chemistry 171

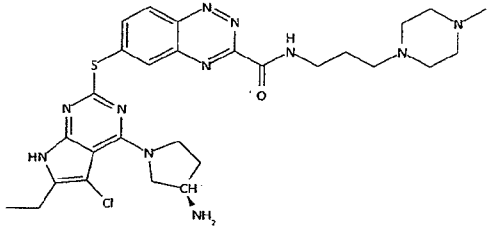
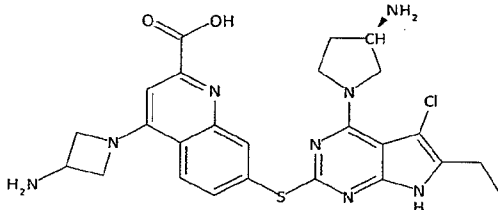
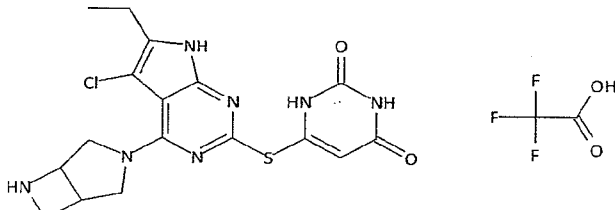
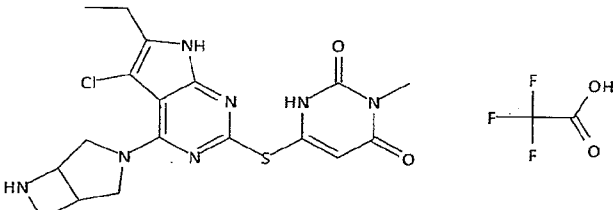
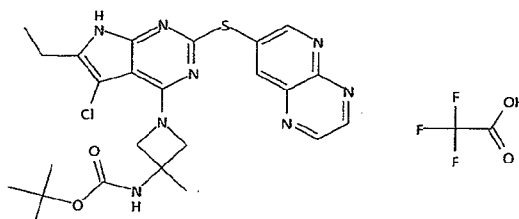
Rx ID	CHEMISTRY
700,586	 Chemistry 172
700,587	 Chemistry 173
700,588	 Chemistry 174
700,589	 Chemistry 175
700,590	 Chemistry 176

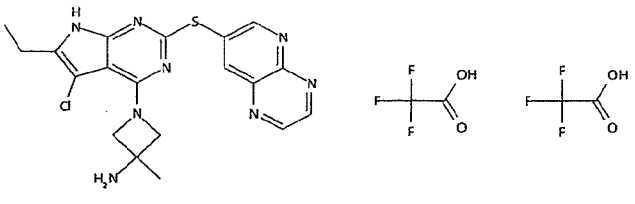
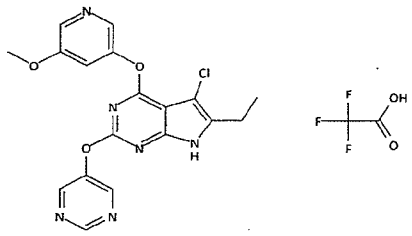
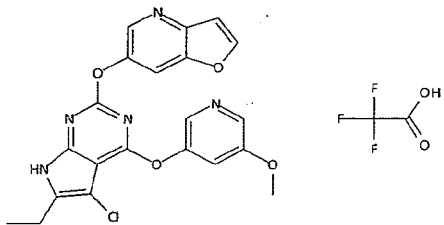
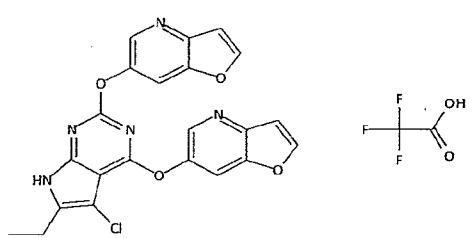
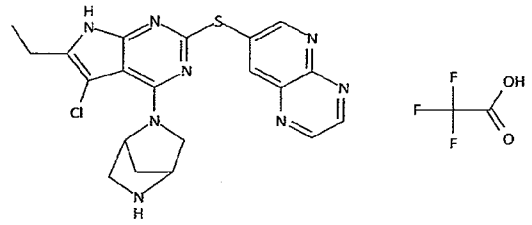
Rx ID	CHEMISTRY
700,592	 Chemistry 177
700,595	 Chemistry 178
700,596	 Chemistry 179
700,597	 Chemistry 180
700,601	 Chemistry 181

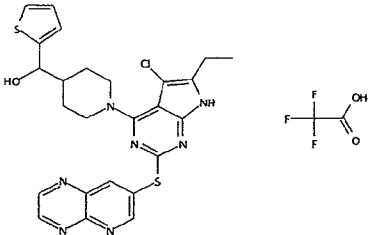
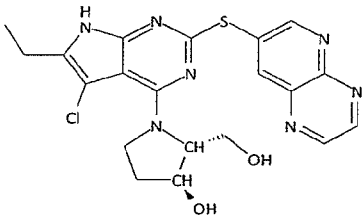
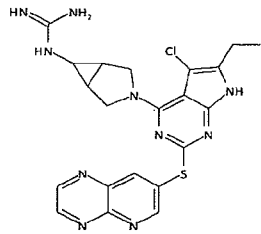
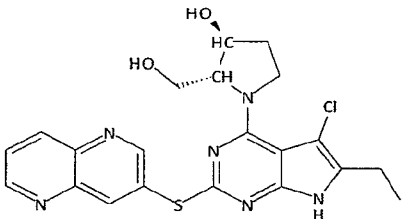
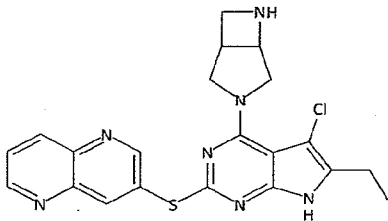
Rx ID	CHEMISTRY
700,602	 Chemistry 182
700,603	 Chemistry 183
700,604	 Chemistry 184
700,605	 Chemistry 185
700,606	 Chemistry 186

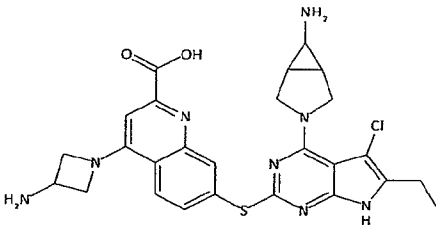
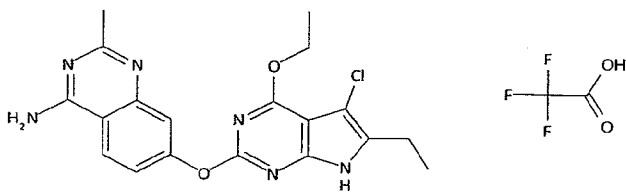
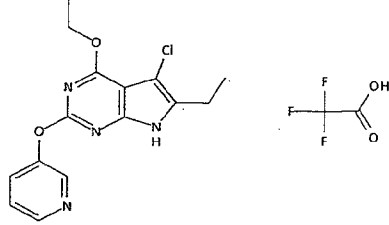
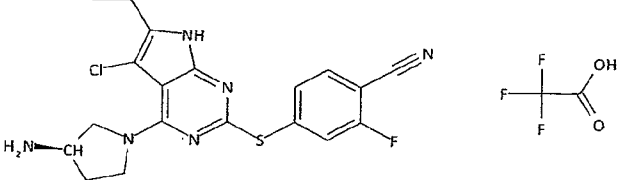
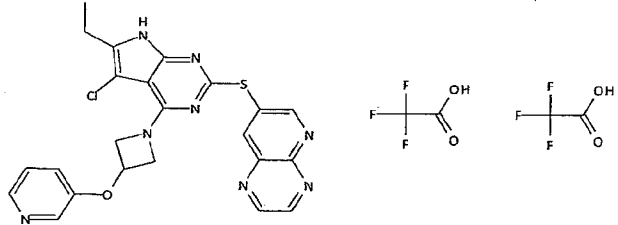
Rx ID	CHEMISTRY
700,607	 Chemistry 187
700,608	 Chemistry 188
700,609	 Chemistry 189
700,611	 Chemistry 190
700,612	 Chemistry 191

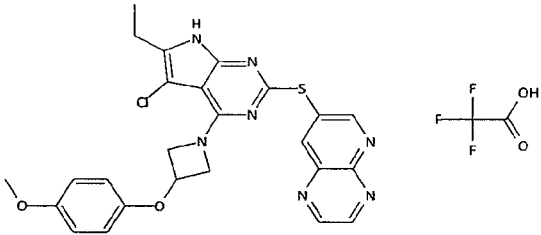
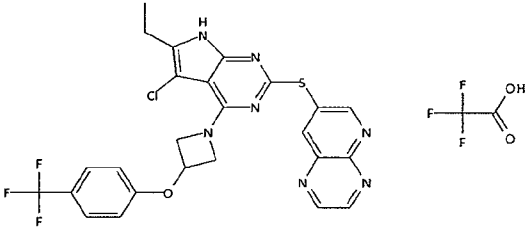
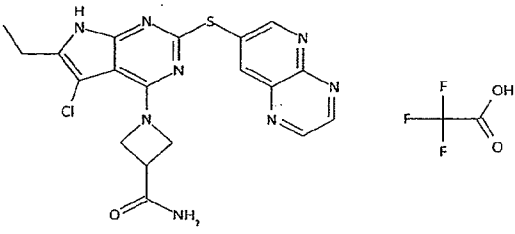
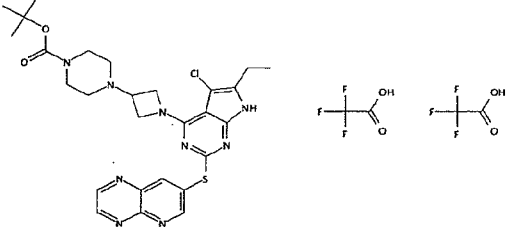
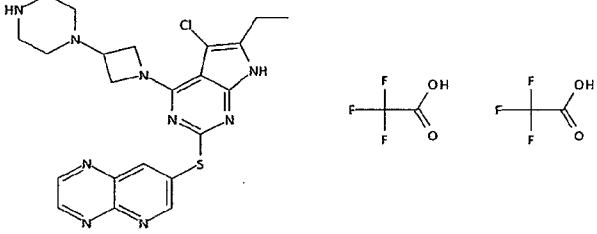
Rx ID	CHEMISTRY
700,613	 Chemistry 192
700,614	 Chemistry 193
700,615	 Chemistry 194
700,617	 Chemistry 195
700,618	 Chemistry 196

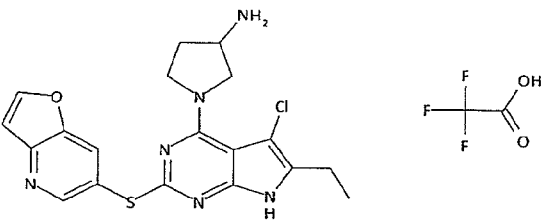
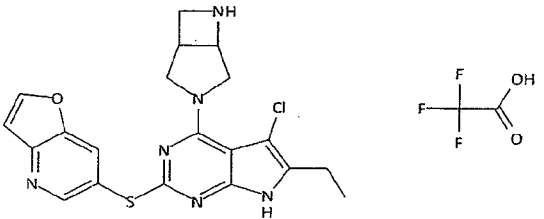
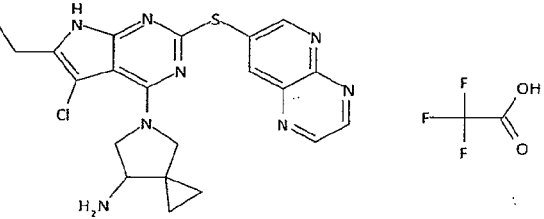
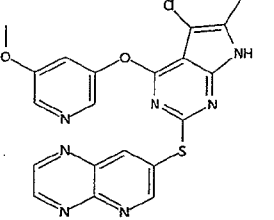
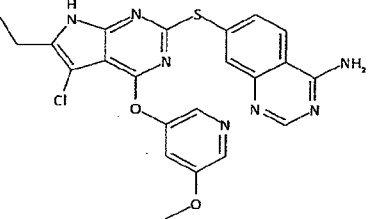
Rx ID	CHEMISTRY
700,619	 Chemistry 197
700,620	 Chemistry 198
700,627	 Chemistry 199
700,628	 Chemistry 200
700,629	 Chemistry 201

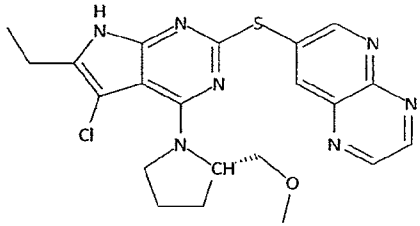
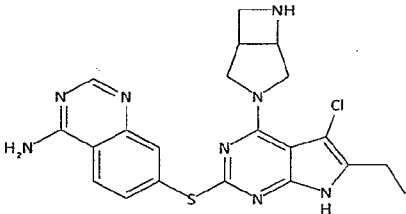
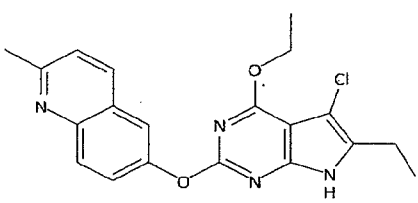
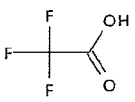
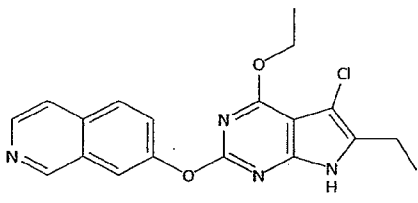
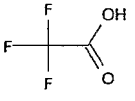
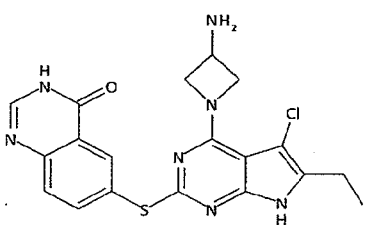
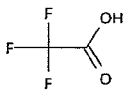
Rx ID	CHEMISTRY
700,630	 Chemistry 202
700,648	 Chemistry 203
700,649	 Chemistry 204
700,650	 Chemistry 205
700,655	 Chemistry 206

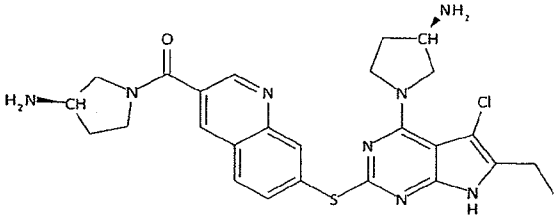
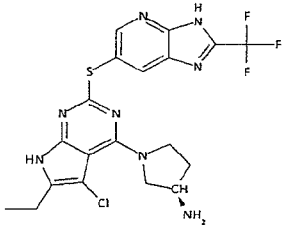
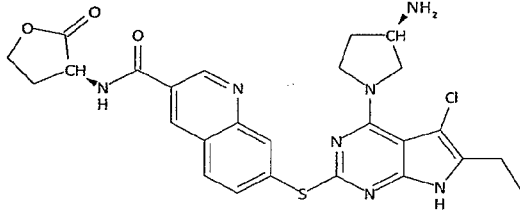
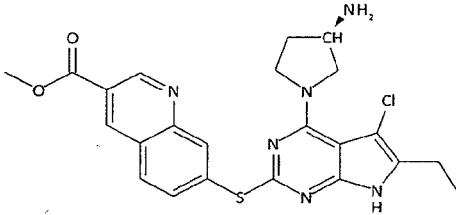
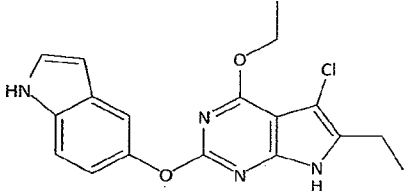
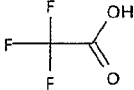
Rx ID	CHEMISTRY
700,656	 Chemistry 207
700,657	 Chemistry 208
700,658	 Chemistry 209
700,659	 Chemistry 210
700,660	 Chemistry 211

Rx ID	CHEMISTRY
700,661	 Chemistry 212
700,664	 Chemistry 213
700,665	 Chemistry 214
700,666	 Chemistry 215
700,667	 Chemistry 216

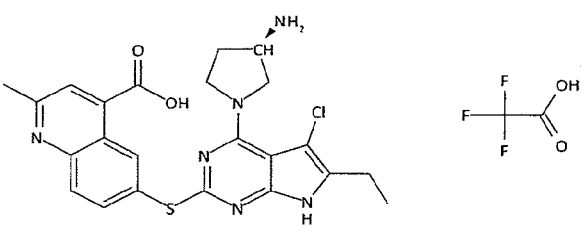
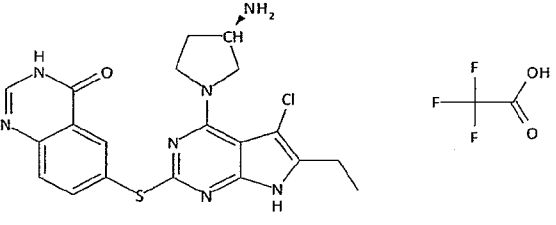
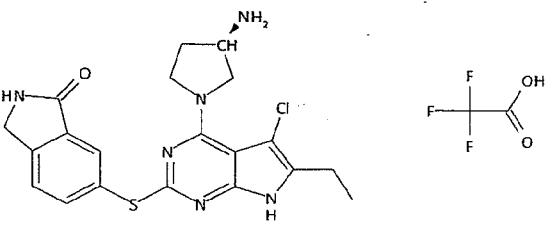
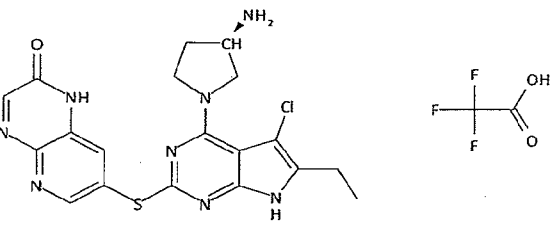
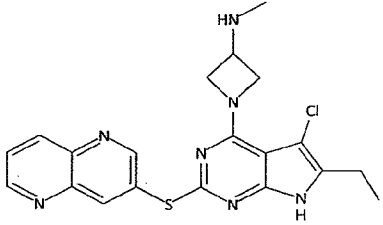
Rx ID	CHEMISTRY
700,668	 Chemistry 217
700,669	 Chemistry 218
700,670	 Chemistry 219
700,671	 Chemistry 220
700,672	 Chemistry 221

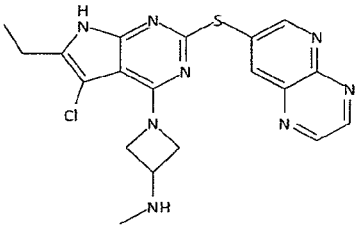
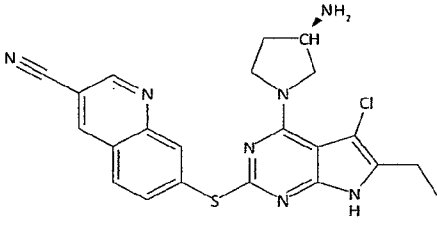
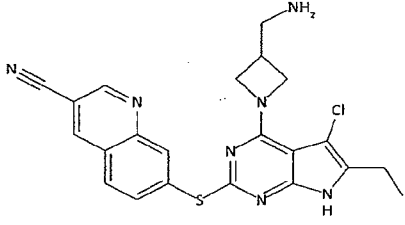
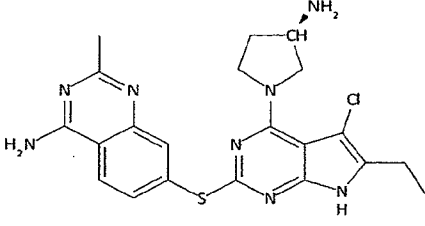
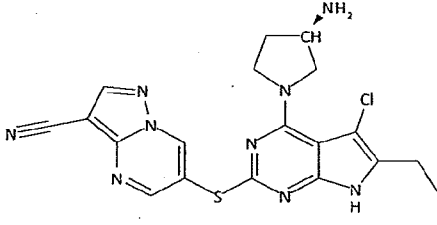
Rx ID	CHEMISTRY
700,676	 Chemistry 222
700,677	 Chemistry 223
700,678	 Chemistry 224
700,686	 Chemistry 225
700,687	 Chemistry 226

Rx ID	CHEMISTRY
700,688	 Chemistry 227
700,689	 Chemistry 228
700,690	  Chemistry 229
700,691	  Chemistry 230
700,694	  Chemistry 231

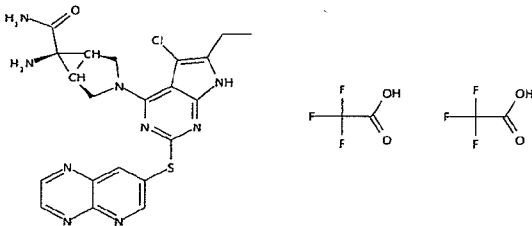
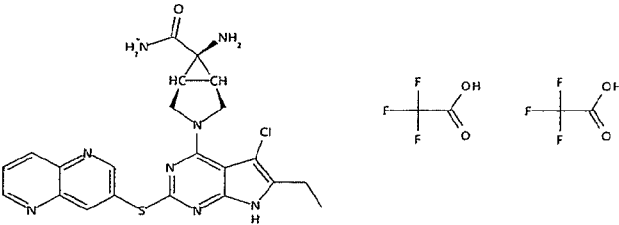
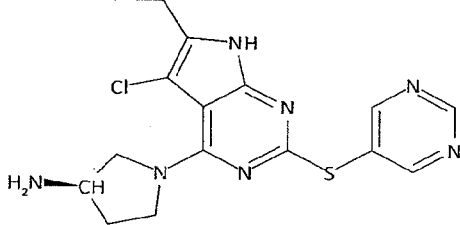
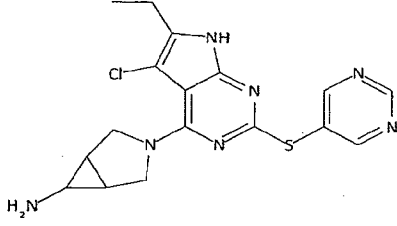
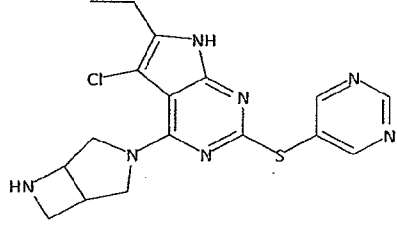
Rx ID	CHEMISTRY
700,695	 Chemistry 232
700,696	 Chemistry 233
700,697	 Chemistry 234
700,698	 Chemistry 235
700,699	  Chemistry 236

Rx ID	CHEMISTRY
700,700	 Chemistry 237
700,702	 Chemistry 238
700,705	 Chemistry 239
700,706	 Chemistry 240
700,707	 Chemistry 241

Rx ID	CHEMISTRY
700,708	 Chemistry 242
700,710	 Chemistry 243
700,711	 Chemistry 244
700,712	 Chemistry 245
700,713	 Chemistry 246

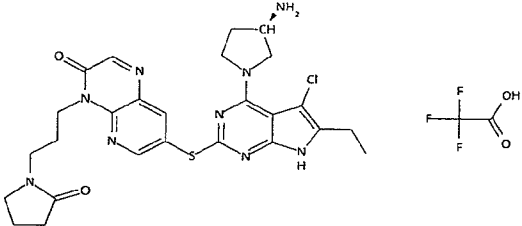
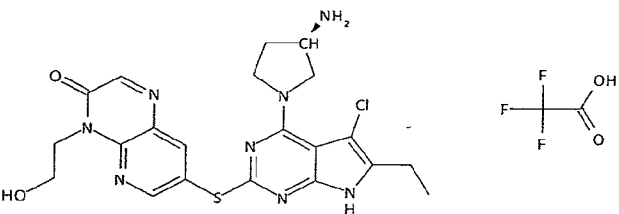
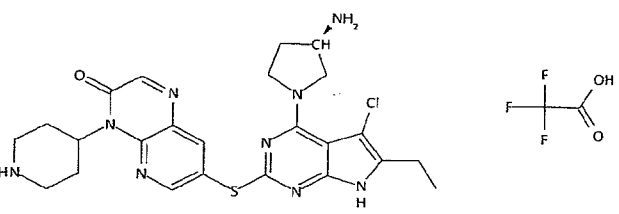
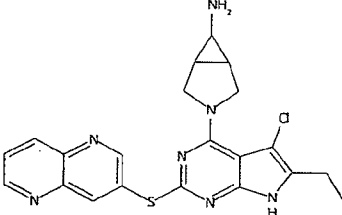
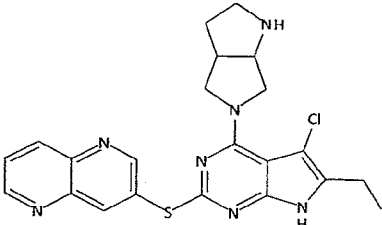
Rx ID	CHEMISTRY
700,714	 Chemistry 247
700,715	 Chemistry 248
700,716	 Chemistry 249
700,717	 Chemistry 250
700,718	 Chemistry 251

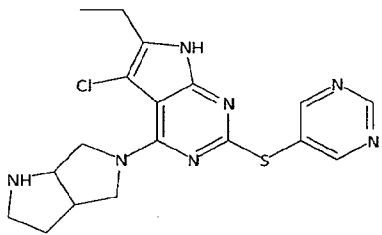
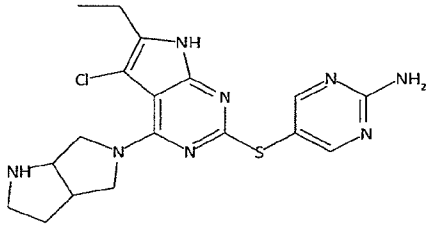
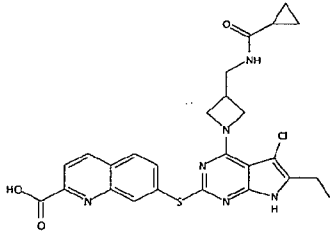
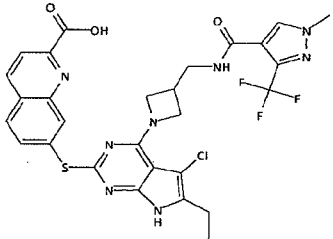
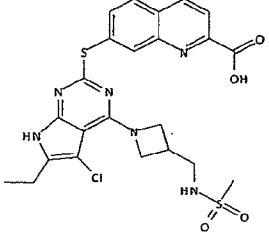
Rx ID	CHEMISTRY
700,719	 Chemistry 252
700,720	 Chemistry 253
700,721	 Chemistry 254
700,722	 Chemistry 255
700,723	 Chemistry 256

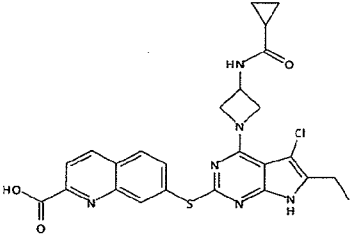
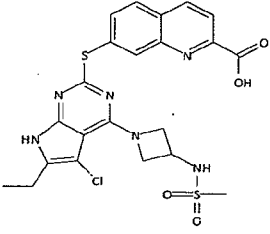
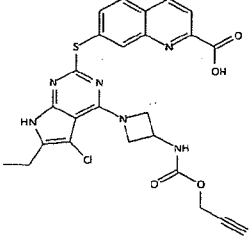
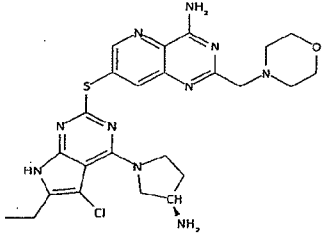
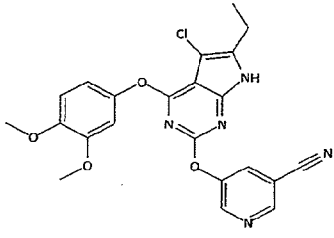
Rx ID	CHEMISTRY
700,781	 Chemistry 257
700,782	 Chemistry 258
700,783	 Chemistry 259
700,784	 Chemistry 260
700,785	 Chemistry 261

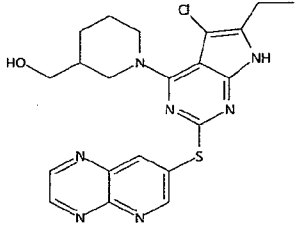
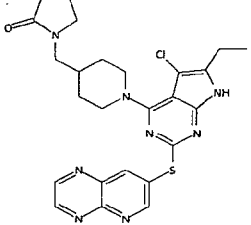
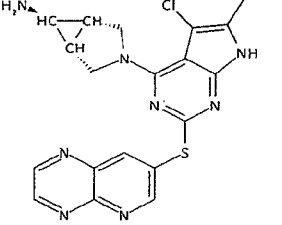
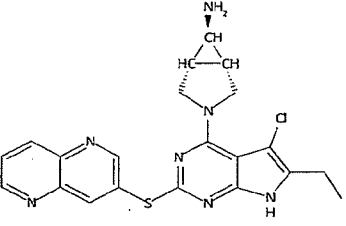
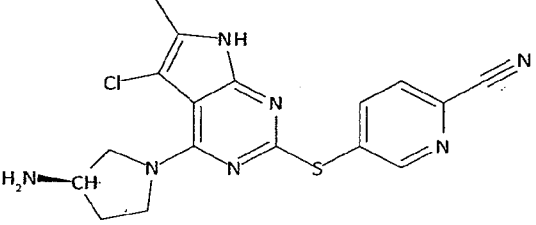
Rx ID	CHEMISTRY
700,786	 Chemistry 262
700,787	 Chemistry 263
700,788	 Chemistry 264
700,789	 Chemistry 265
700,790	 Chemistry 266

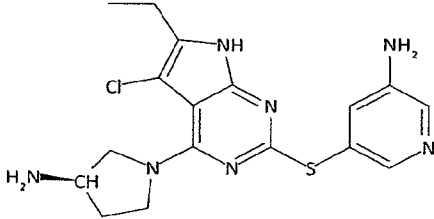
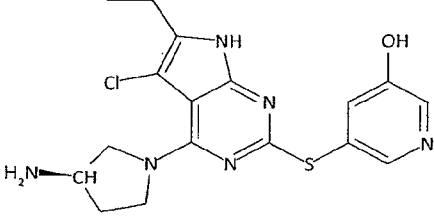
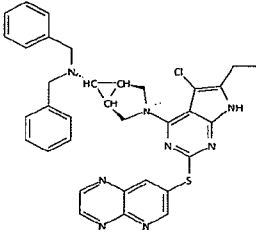
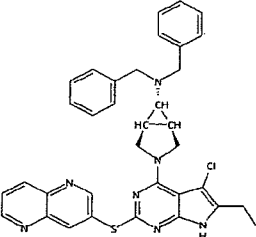
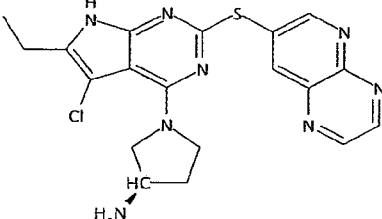
Rx ID	CHEMISTRY
700,791	 Chemistry 267
700,792	 Chemistry 268
700,794	 Chemistry 269
700,795	 Chemistry 270
700,796	 Chemistry 271

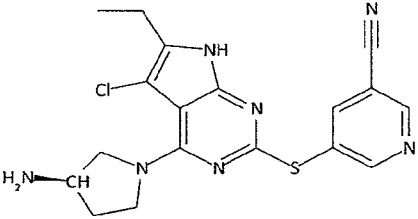
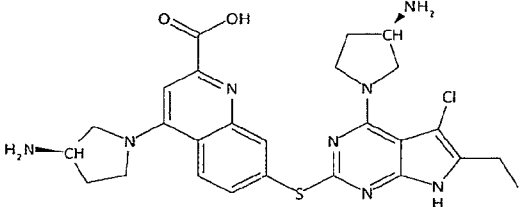
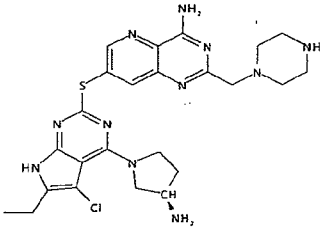
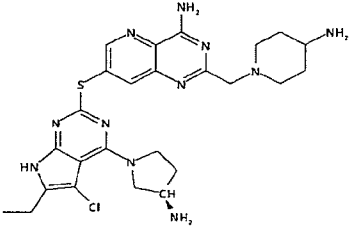
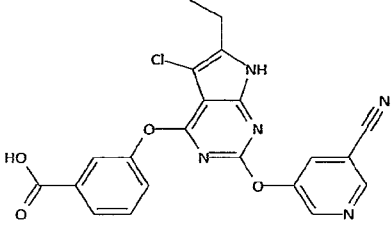
Rx ID	CHEMISTRY
700,797	 Chemistry 272
700,798	 Chemistry 273
700,799	 Chemistry 274
700,800	 Chemistry 275
700,801	 Chemistry 276

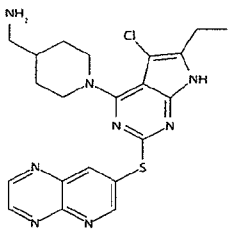
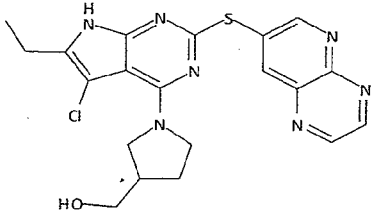
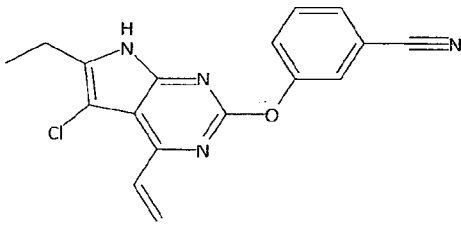
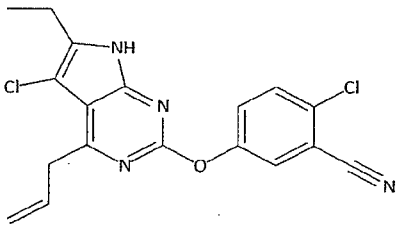
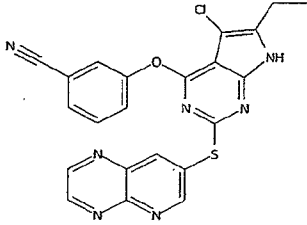
Rx ID	CHEMISTRY
700,802	 Chemistry 277
700,803	 Chemistry 278
700,804	 Chemistry 279
700,805	 Chemistry 280
700,806	 Chemistry 281

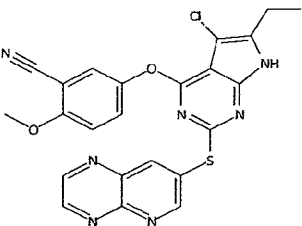
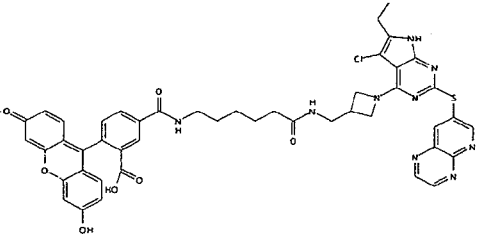
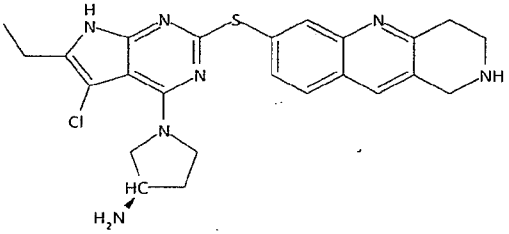
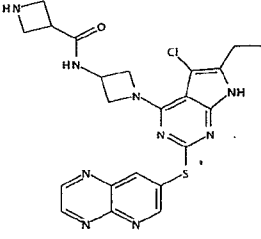
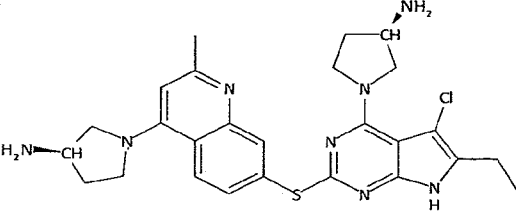
Rx ID	CHEMISTRY
700,807	 Chemistry 282
700,808	 Chemistry 283
700,809	 Chemistry 284
700,812	 Chemistry 285
700,813	 Chemistry 286

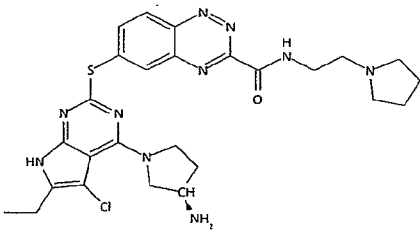
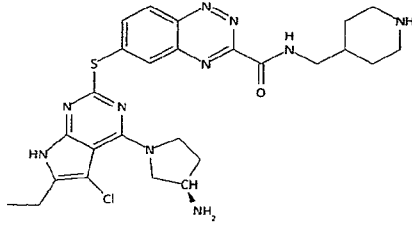
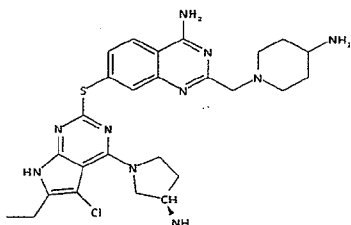
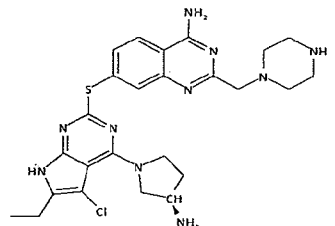
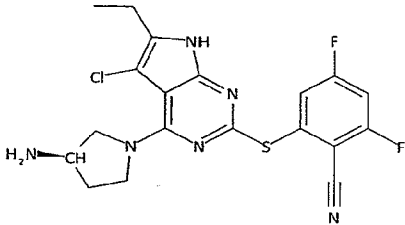
Rx ID	CHEMISTRY
700,814	 Chemistry 287
700,815	 Chemistry 288
700,816	 Chemistry 289
700,817	 Chemistry 290
700,818	 Chemistry 291

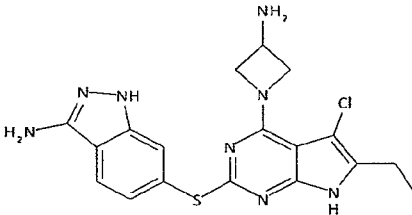
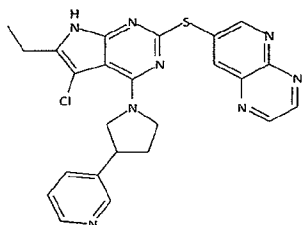
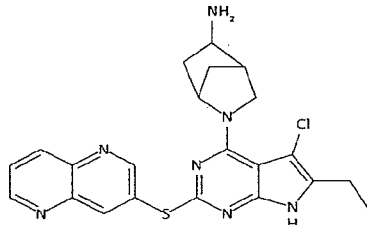
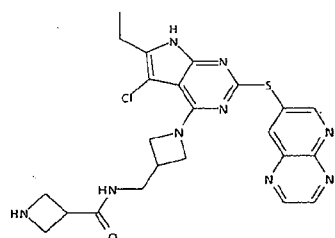
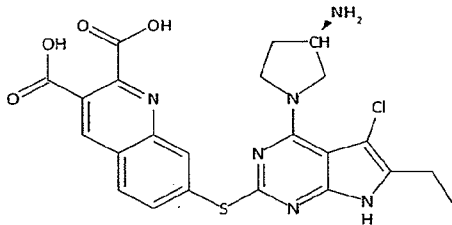
Rx ID	CHEMISTRY
700,820	 Chemistry 292
700,821	 Chemistry 293
700,822	 Chemistry 294
700,823	 Chemistry 295
700618-2	 Chemistry 296

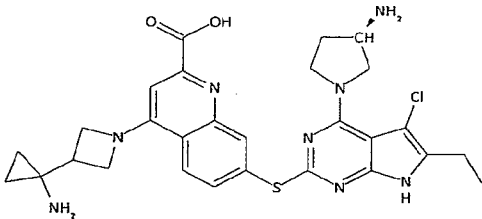
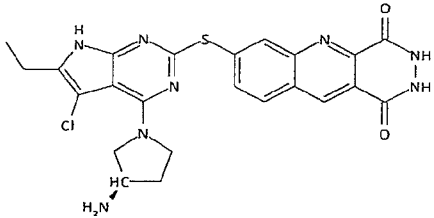
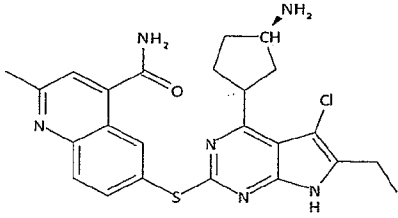
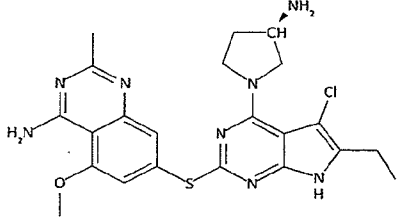
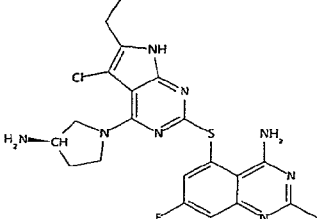
Rx ID	CHEMISTRY
700,824	 Chemistry 297
700,825	 Chemistry 298
700,826	 Chemistry 299
700,827	 Chemistry 300
700,828	 Chemistry 301

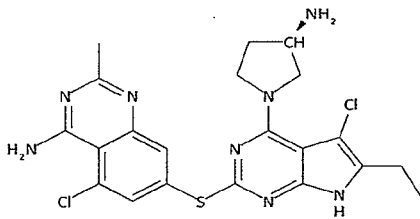
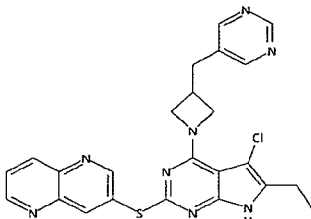
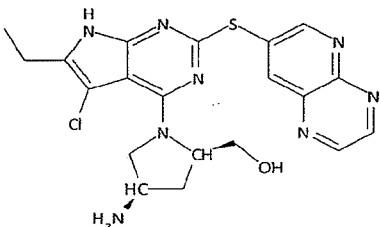
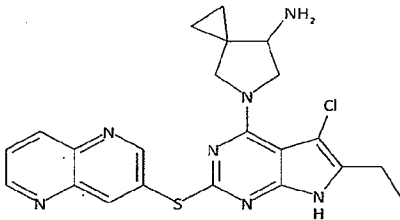
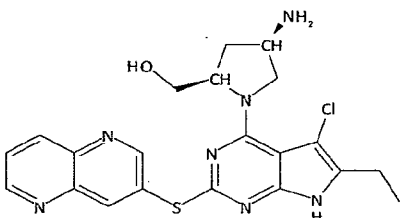
Rx ID	CHEMISTRY
700,829	 Chemistry 302
700,830	 Chemistry 303
700,831	 Chemistry 304
700,832	 Chemistry 305
700,833	 Chemistry 306

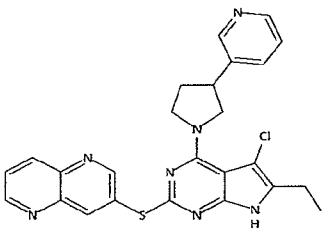
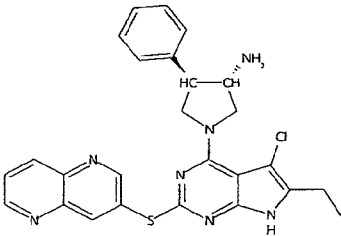
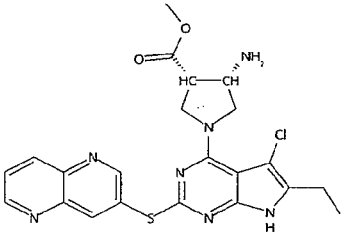
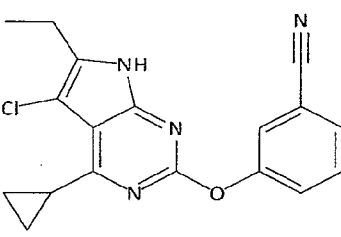
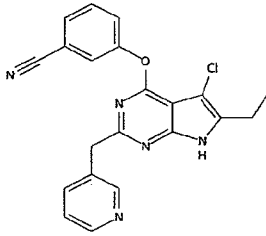
Rx ID	CHEMISTRY
700,834	 Chemistry 307
700,835	 Chemistry 308
700,841	 Chemistry 309
700,842	 Chemistry 310
700,843	 Chemistry 311

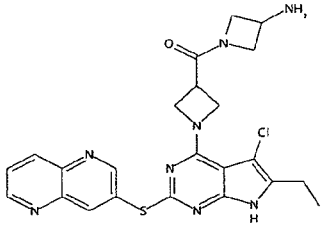
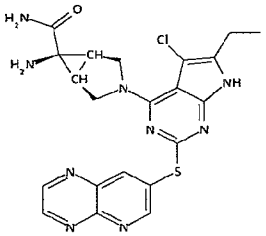
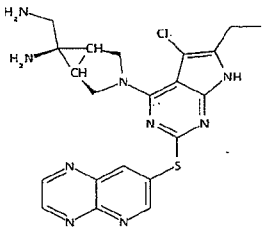
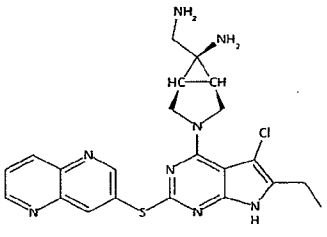
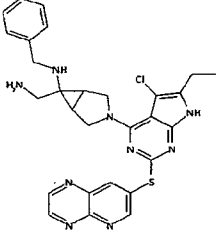
Rx ID	CHEMISTRY
700,844	 Chemistry 312
700,845	 Chemistry 313
700,846	 Chemistry 314
700,847	 Chemistry 315
700,848	 Chemistry 316

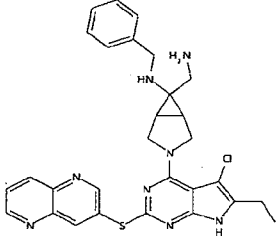
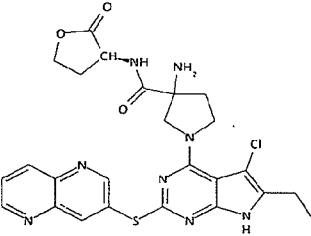
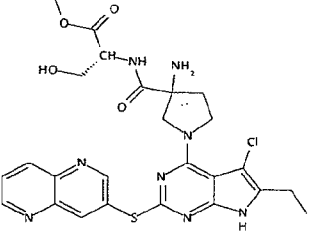
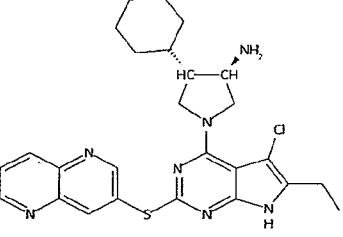
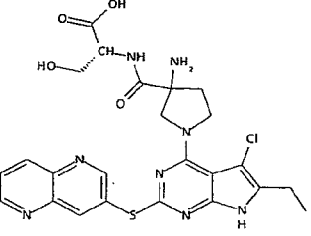
Rx ID	CHEMISTRY
700,850	 Chemistry 317
700,851	 Chemistry 318
700,857	 Chemistry 319
700,858	 Chemistry 320
700,859	 Chemistry 321

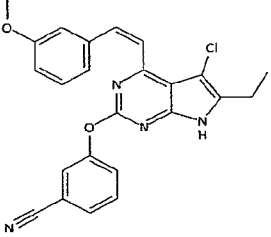
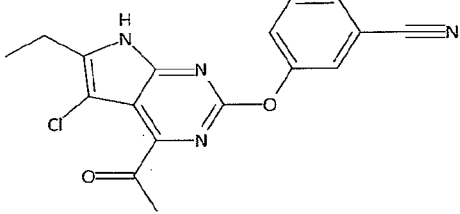
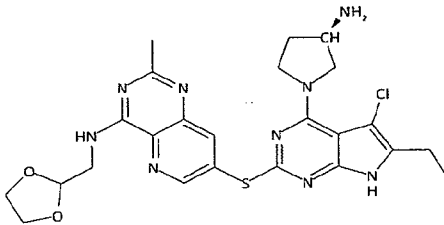
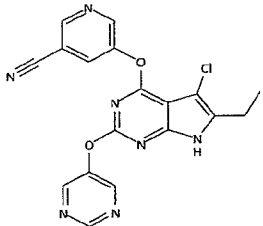
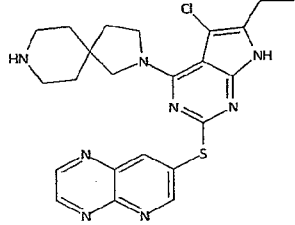
Rx ID	CHEMISTRY
700,860	 Chemistry 322
700,861	 Chemistry 323
700,862	 Chemistry 324
700,863	 Chemistry 325
700,864	 Chemistry 326

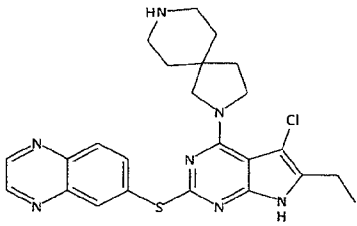
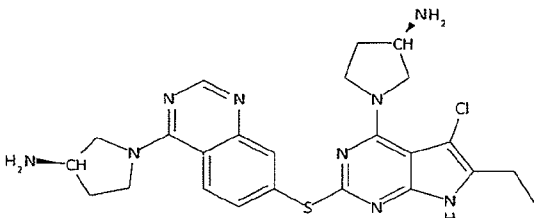
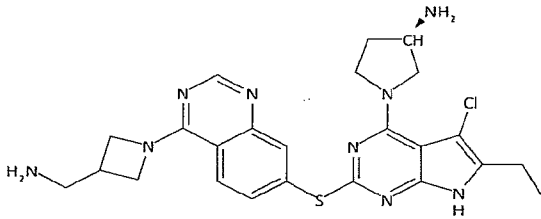
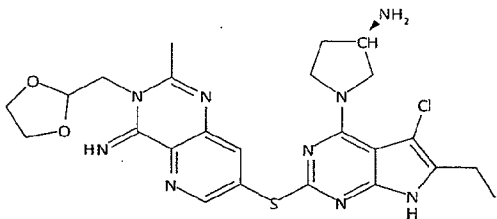
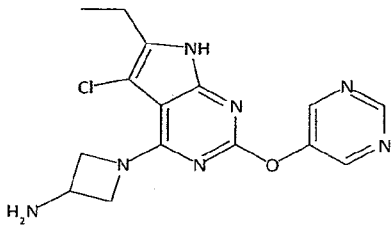
Rx ID	CHEMISTRY
700,865	 Chemistry 327
700,867	 Chemistry 328
700,868	 Chemistry 329
700,869	 Chemistry 330
700,870	 Chemistry 331

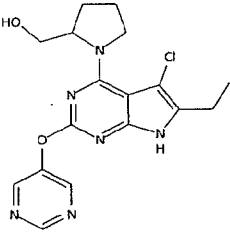
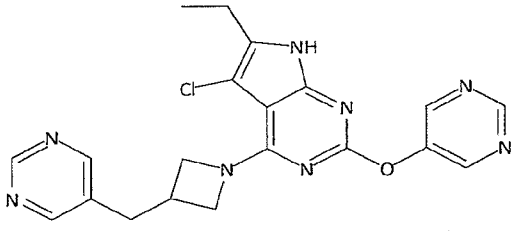
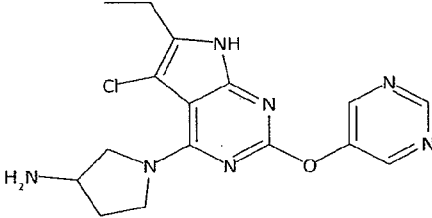
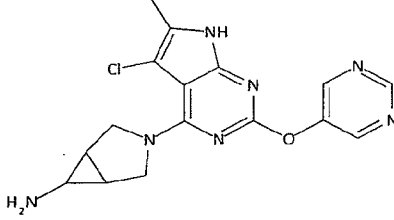
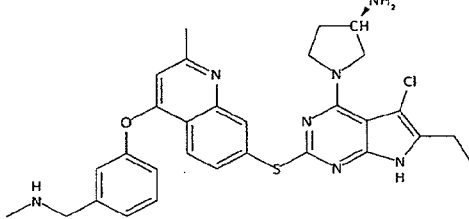
Rx ID	CHEMISTRY
700,871	 Chemistry 332
700,872	 Chemistry 333
700,873	 Chemistry 334
700,874	 Chemistry 335
700,875	 Chemistry 336

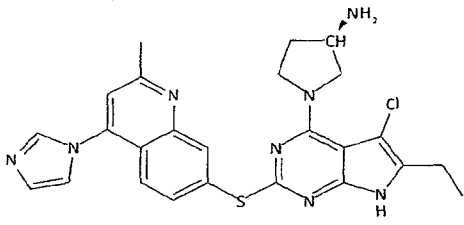
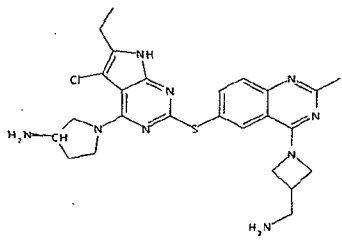
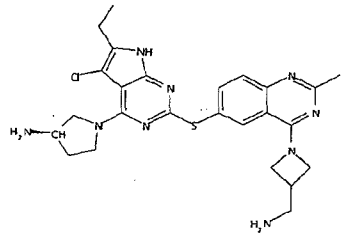
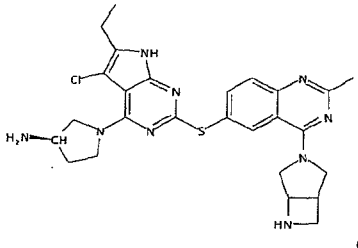
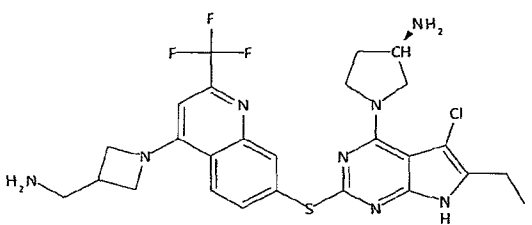
Rx ID	CHEMISTRY
700,876	 Chemistry 337
700781-2	 Chemistry 338
700,884	 Chemistry 339
700,885	 Chemistry 340
700,886	 Chemistry 341

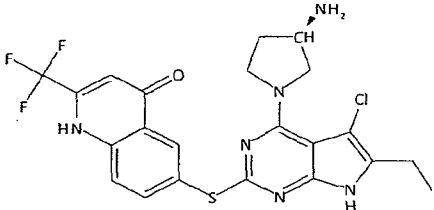
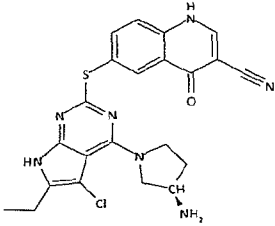
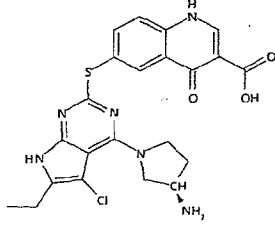
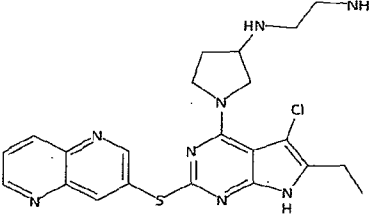
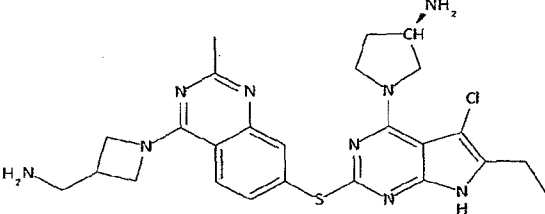
Rx ID	CHEMISTRY
700,887	 Chemistry 342
700,888	 Chemistry 343
700,889	 Chemistry 344
700,890	 Chemistry 345
700,891	 Chemistry 346

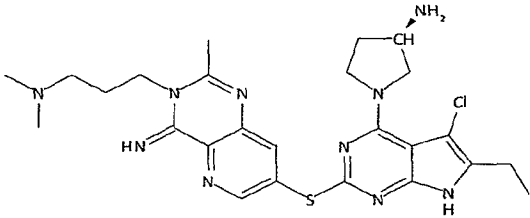
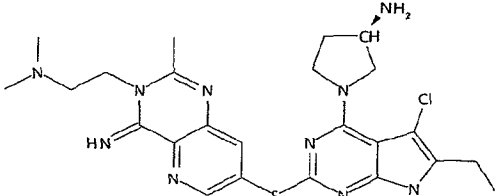
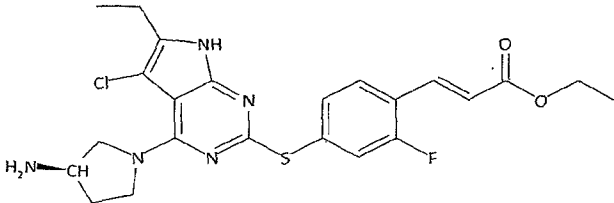
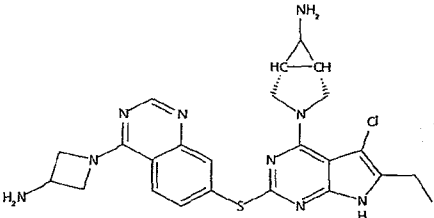
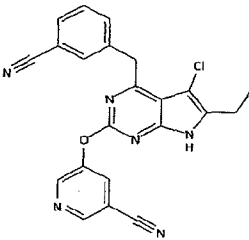
Rx ID	CHEMISTRY
700,892	 Chemistry 347
700,893	 Chemistry 348
700,894	 Chemistry 349
700,898	 Chemistry 350
700,900	 Chemistry 351

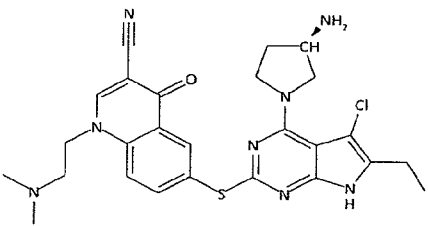
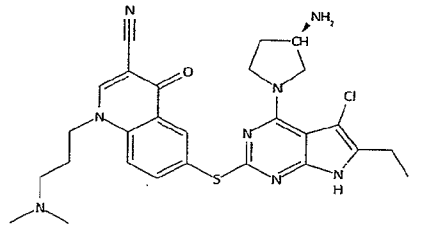
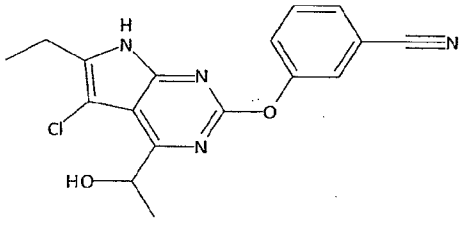
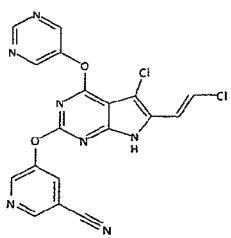
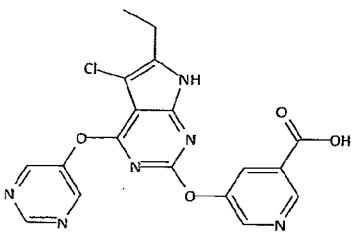
Rx ID	CHEMISTRY
700,901	 Chemistry 352
700,903	 Chemistry 353
700,904	 Chemistry 354
700,906	 Chemistry 355
700,907	 Chemistry 356

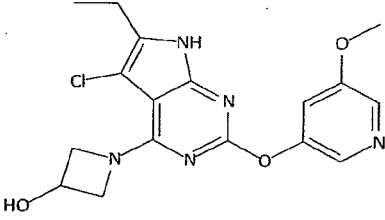
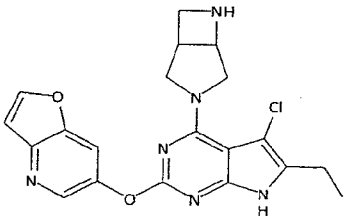
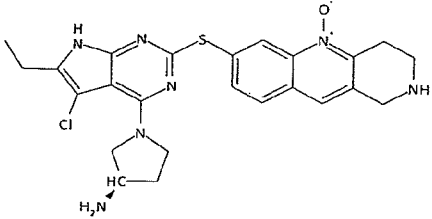
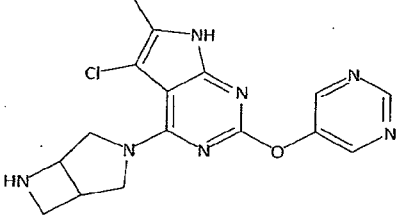
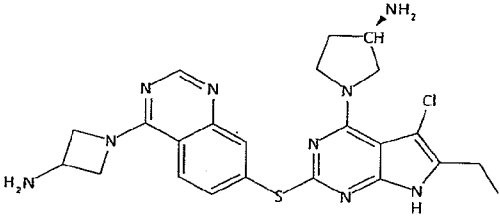
Rx ID	CHEMISTRY
700,908	 Chemistry 357
700,909	 Chemistry 358
700,910	 Chemistry 359
700,911	 Chemistry 360
700,912	 Chemistry 361

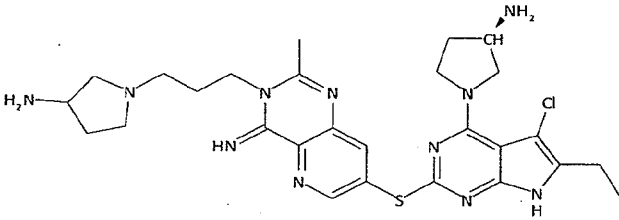
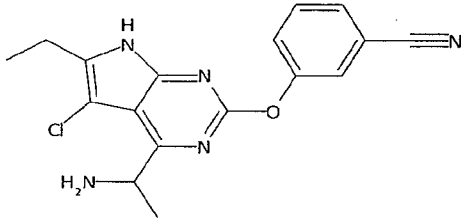
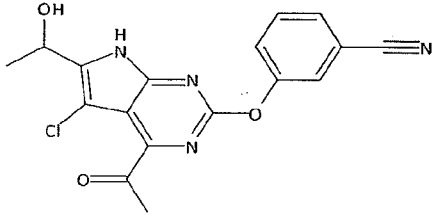
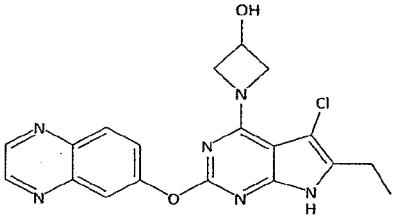
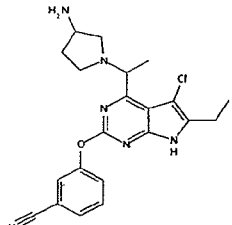
Rx ID	CHEMISTRY
700,913	 Chemistry 362
700,914	 Chemistry 363
700,915	 Chemistry 364
700,916	 Chemistry 365
700,917	 Chemistry 366

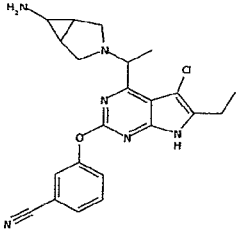
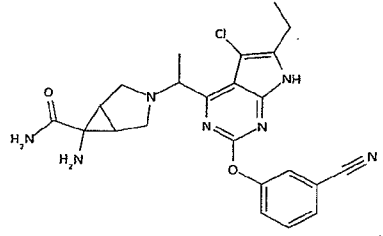
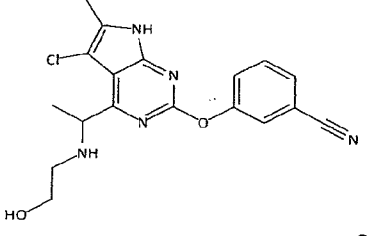
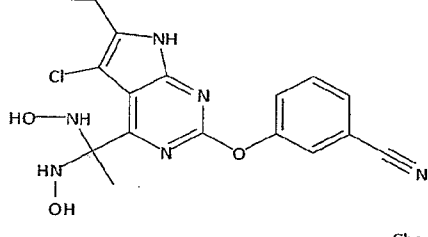
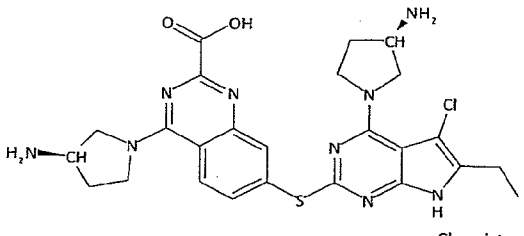
Rx ID	CHEMISTRY
700,918	 Chemistry 367
700,919	 Chemistry 368
700,920	 Chemistry 369
700,921	 Chemistry 370
700,922	 Chemistry 371

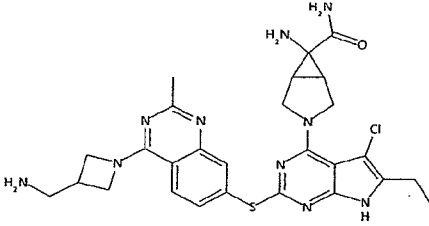
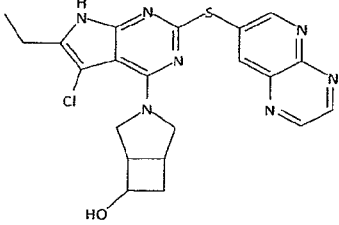
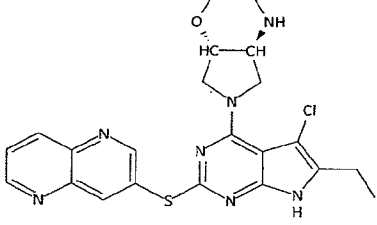
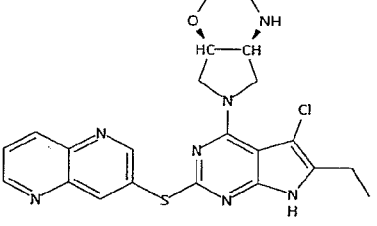
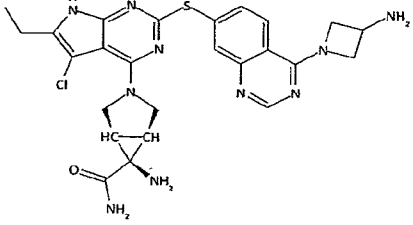
Rx ID	CHEMISTRY
700,923	 Chemistry 372
700,924	 Chemistry 373
700,925	 Chemistry 374
700,926	 Chemistry 375
700,927	 Chemistry 376

Rx ID	CHEMISTRY
700,928	 Chemistry 377
700,929	 Chemistry 378
700,930	 Chemistry 379
700,931	 Chemistry 380
700,932	 Chemistry 381

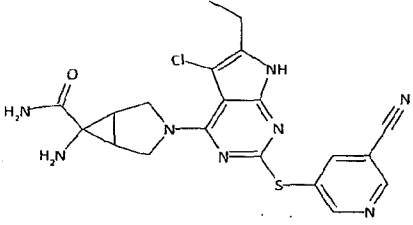
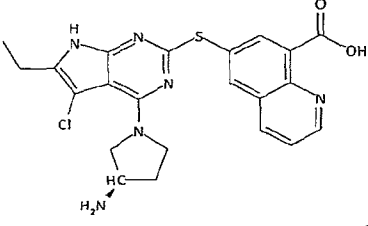
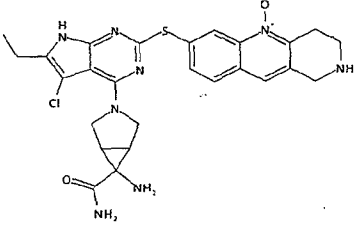
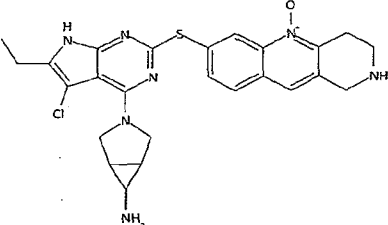
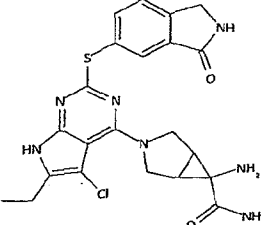
Rx ID	CHEMISTRY
700,934	 Chemistry 382
700,936	 Chemistry 383
700,940	 Chemistry 384
700,941	 Chemistry 385
700,942	 Chemistry 386

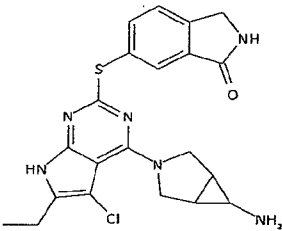
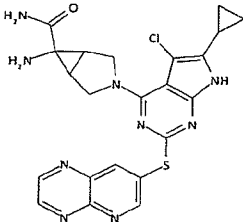
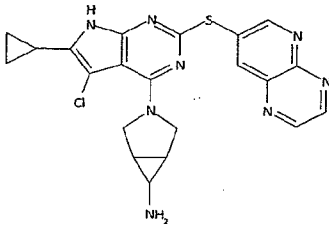
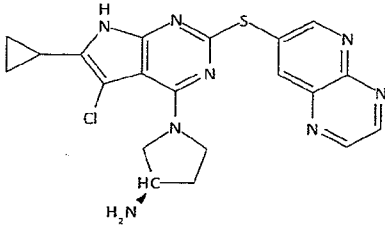
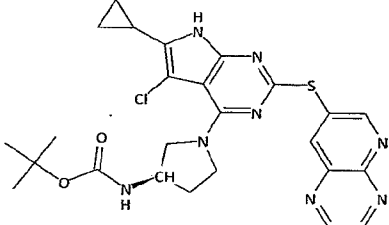
Rx ID	CHEMISTRY
700,943	 Chemistry 387
700,946	 Chemistry 388
700,947	 Chemistry 389
700,948	 Chemistry 390
700,950	 Chemistry 391

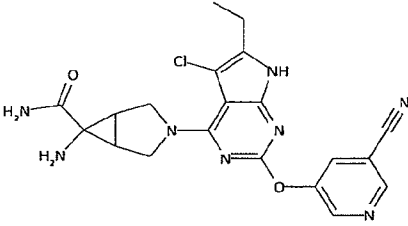
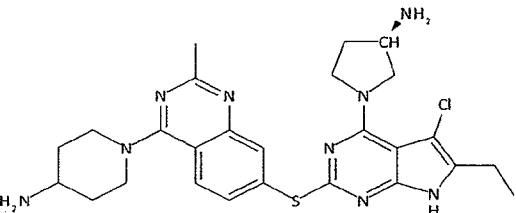
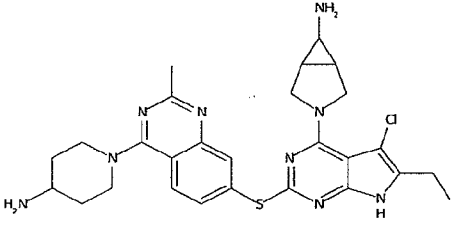
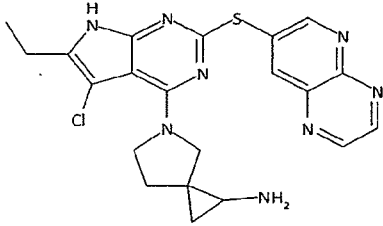
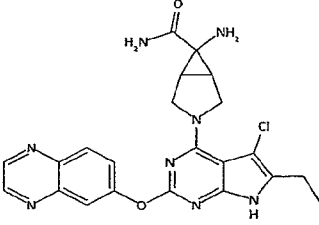
Rx ID	CHEMISTRY
700,951	 Chemistry 392
700,952	 Chemistry 393
700,953	 Chemistry 394
700,954	 Chemistry 395
700,955	 Chemistry 396

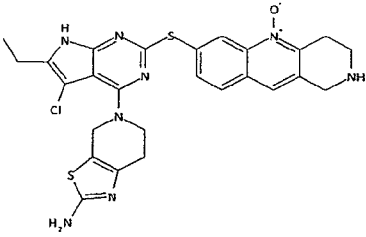
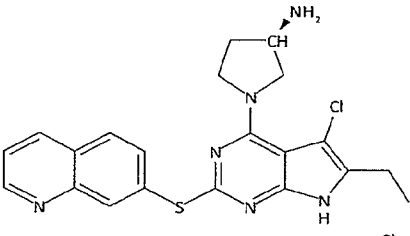
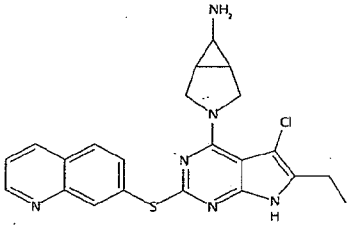
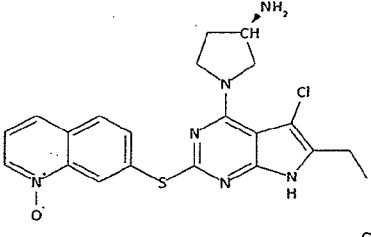
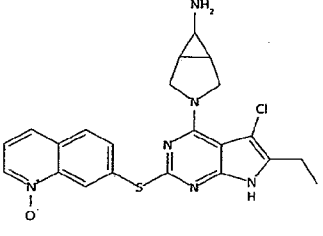
Rx ID	CHEMISTRY
700,956	 Chemistry 397
700,957	 Chemistry 398
700,958	 Chemistry 399
700,959	 Chemistry 400
700,960	 Chemistry 401

Rx ID	CHEMISTRY
700,961	 Chemistry 402
700,962	 Chemistry 403
700,963	 Chemistry 404
700,967	 Chemistry 405
700,968	 Chemistry 406

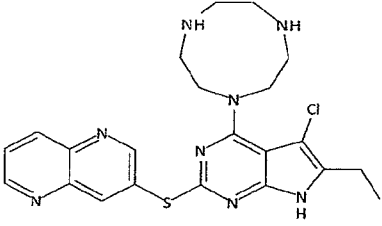
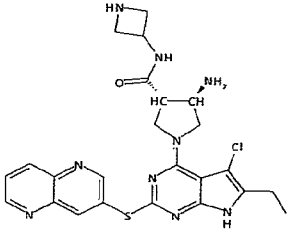
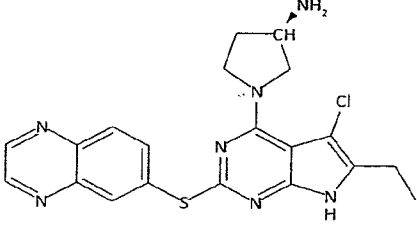
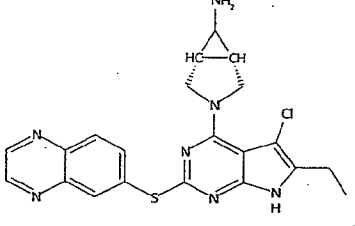
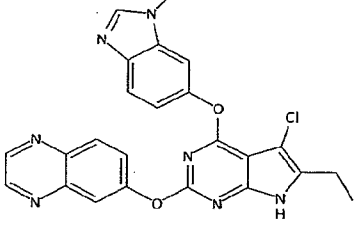
Rx ID	CHEMISTRY
700,969	 Chemistry 407
700,970	 Chemistry 408
700,971	 Chemistry 409
700,972	 Chemistry 410
700,973	 Chemistry 411

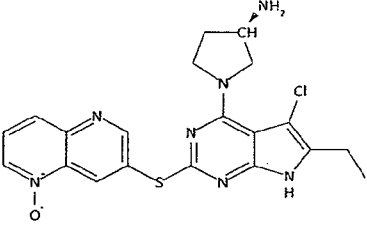
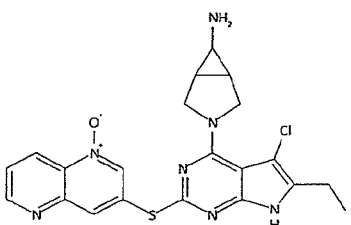
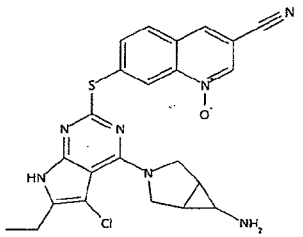
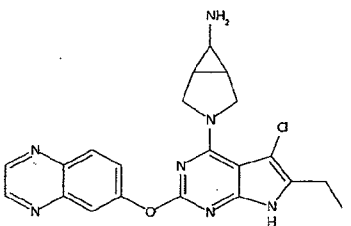
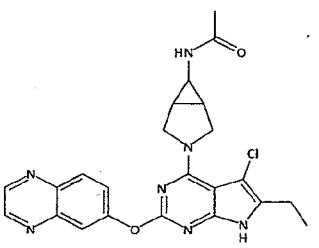
Rx ID	CHEMISTRY
700,974	 Chemistry 412
700,975	 Chemistry 413
700,976	 Chemistry 414
700,977	 Chemistry 415
700,978	 Chemistry 416

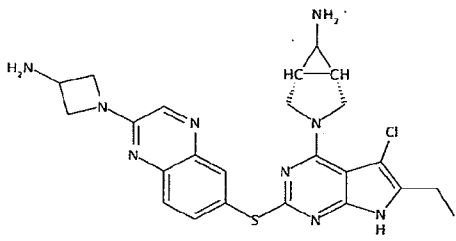
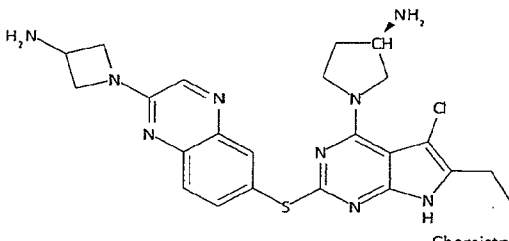
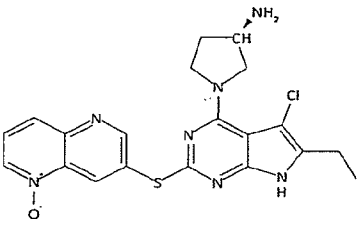
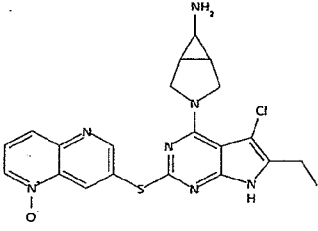
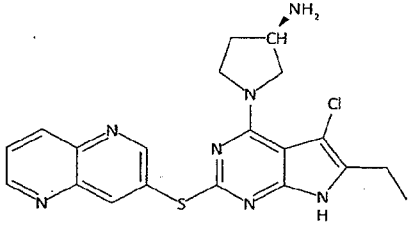
Rx ID	CHEMISTRY
700,981	 Chemistry 417
700,983	 Chemistry 418
700,984	 Chemistry 419
700,986	 Chemistry 420
700,989	 Chemistry 421

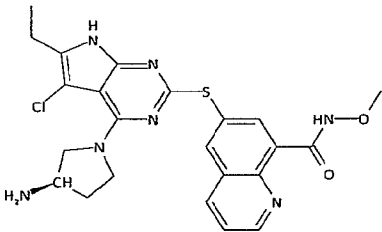
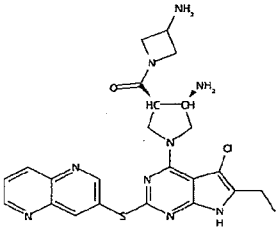
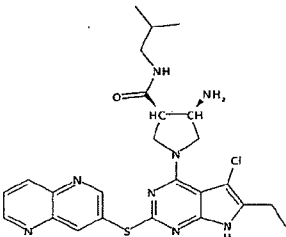
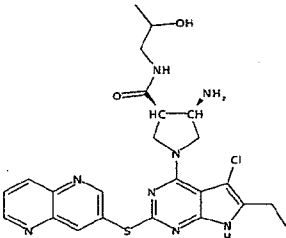
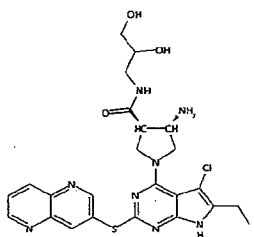
Rx ID	CHEMISTRY
700,990	 Chemistry 422
700,991	 Chemistry 423
700,992	 Chemistry 424
700,993	 Chemistry 425
700,994	 Chemistry 426

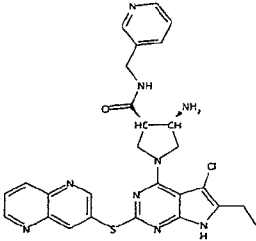
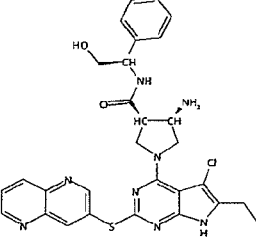
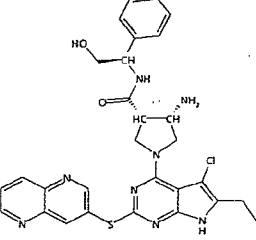
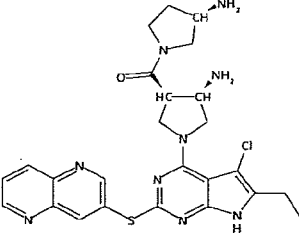
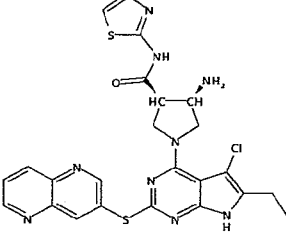
Rx ID	CHEMISTRY
700,995	 Chemistry 427
700,999	 Chemistry 428
701,000	 Chemistry 429
701,001	 Chemistry 430
701,002	 Chemistry 431

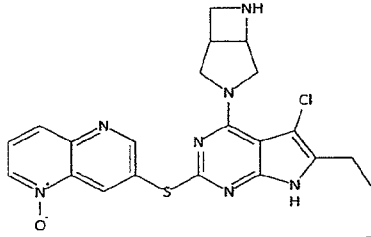
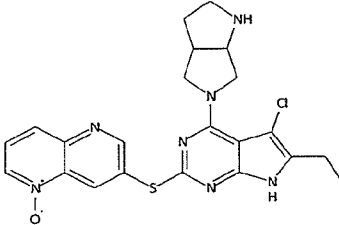
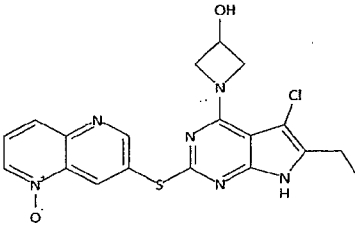
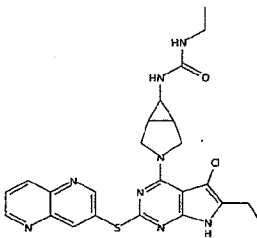
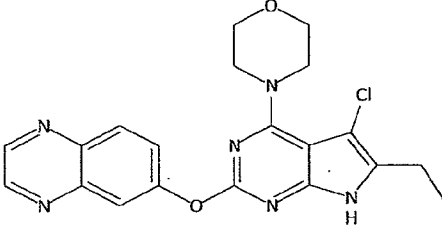
Rx ID	CHEMISTRY
701,003	 Chemistry 432
701,004	 Chemistry 433
701,005	 Chemistry 434
701,006	 Chemistry 435
701,007	 Chemistry 436

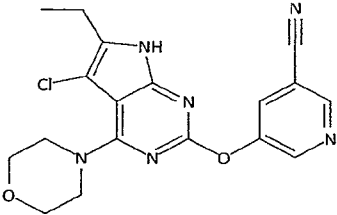
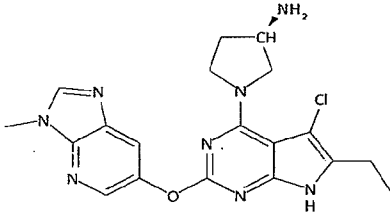
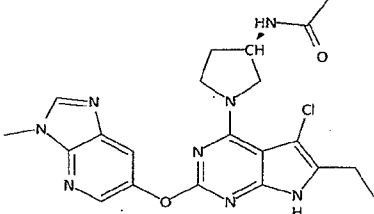
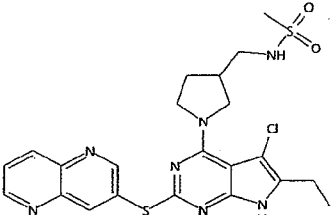
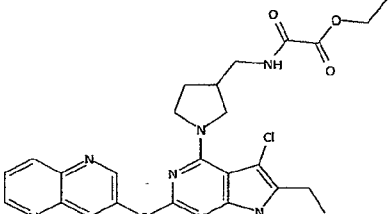
Rx ID	CHEMISTRY
701,008	 Chemistry 437
701,009	 Chemistry 438
701,010	 Chemistry 439
701,011	 Chemistry 440
701,012	 Chemistry 441

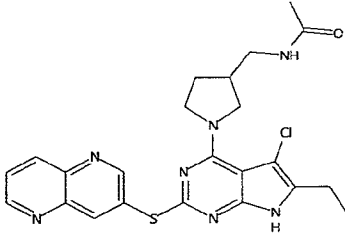
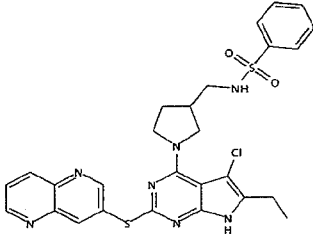
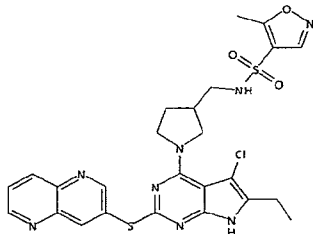
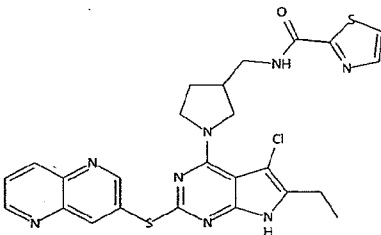
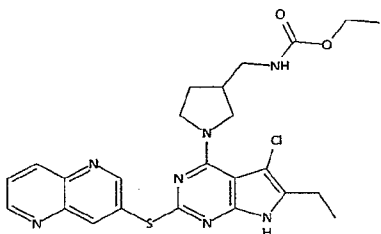
Rx ID	CHEMISTRY
701,013	 Chemistry 442
701,014	 Chemistry 443
701008-2	 Chemistry 444
701009-2	 Chemistry 445
700795-2	 Chemistry 446

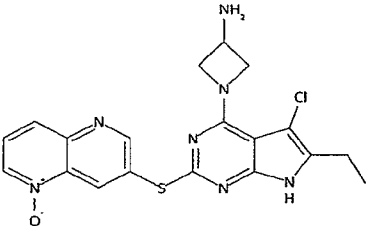
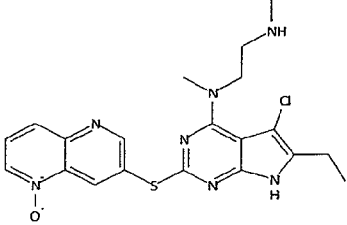
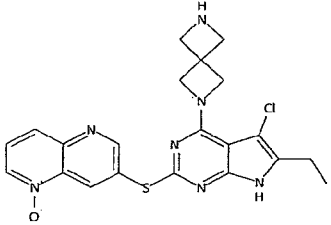
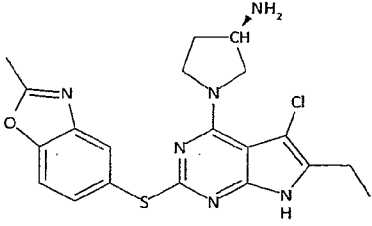
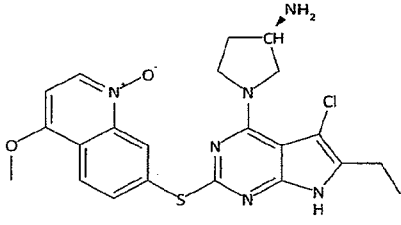
Rx ID	CHEMISTRY
701,015	 Chemistry 447
701,016	 Chemistry 448
701,017	 Chemistry 449
701,018	 Chemistry 450
701,019	 Chemistry 451

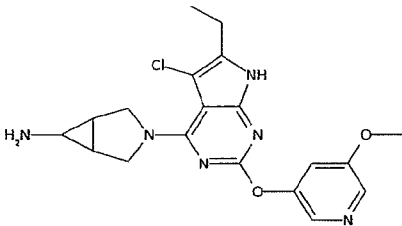
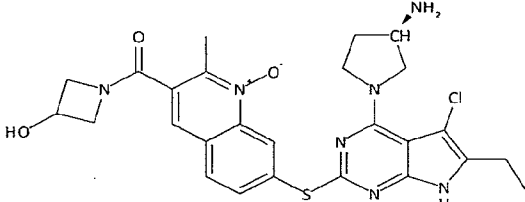
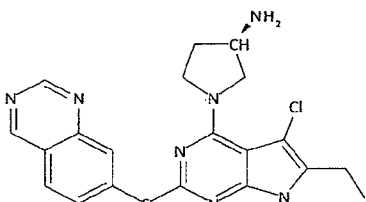
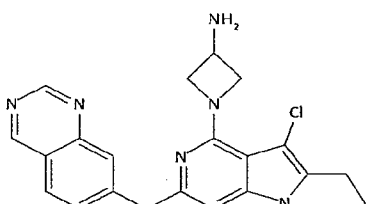
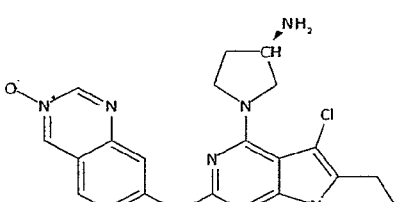
Rx ID	CHEMISTRY
701,020	 Chemistry 452
701,021	 Chemistry 453
701,022	 Chemistry 454
701,023	 Chemistry 455
701,024	 Chemistry 456

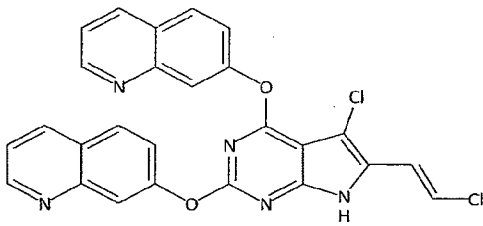
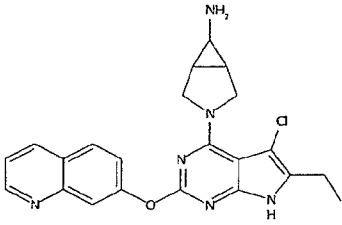
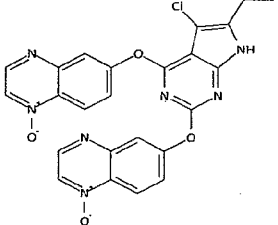
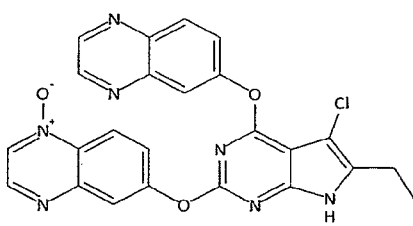
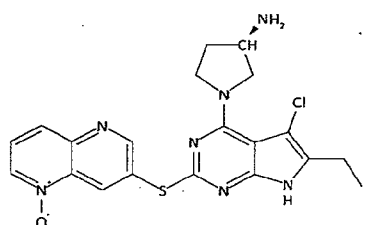
Rx ID	CHEMISTRY
701,025	 Chemistry 457
701,026	 Chemistry 458
701,027	 Chemistry 459
701,028	 Chemistry 460
701,029	 Chemistry 461

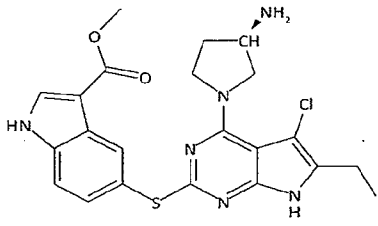
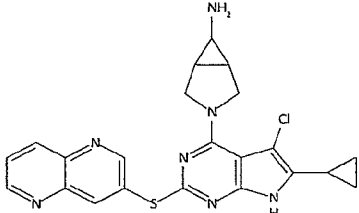
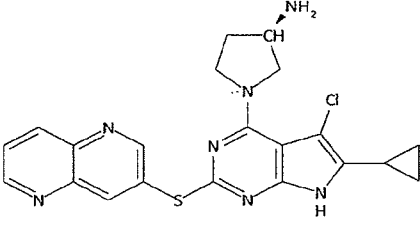
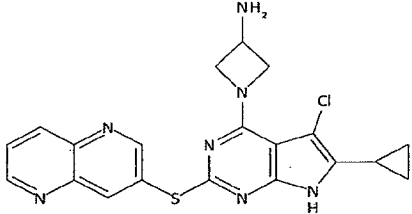
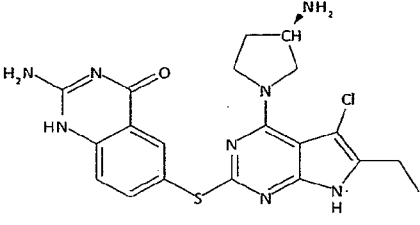
Rx ID	CHEMISTRY
701,031	 Chemistry 462
701,033	 Chemistry 463
701,034	 Chemistry 464
701,042	 Chemistry 465
701,043	 Chemistry 466

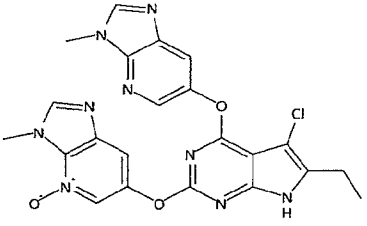
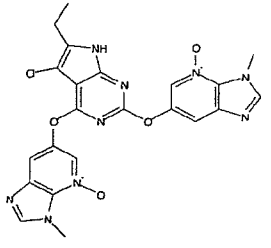
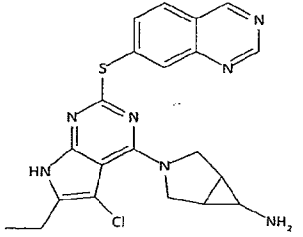
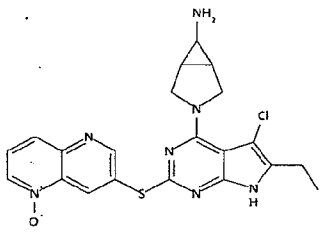
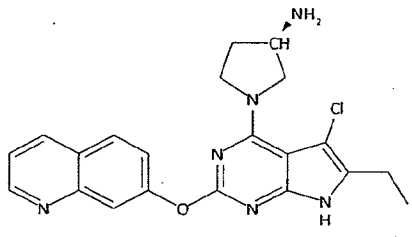
Rx ID	CHEMISTRY
701,044	 Chemistry 467
701,045	 Chemistry 468
701,046	 Chemistry 469
701,047	 Chemistry 470
701,035	 Chemistry 471

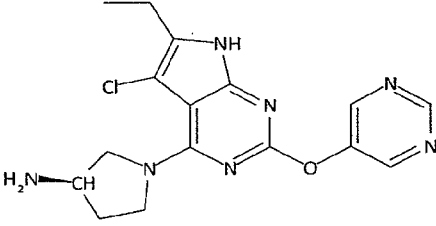
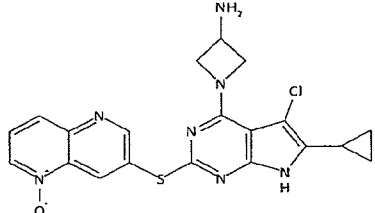
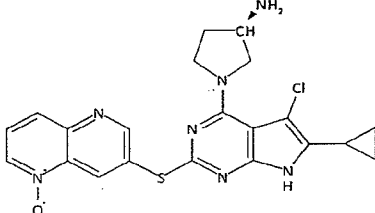
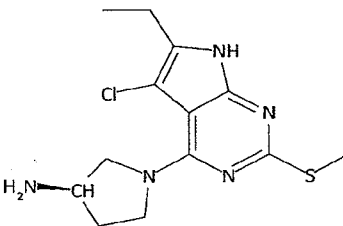
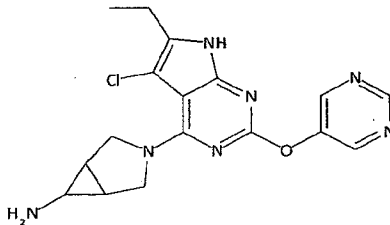
Rx ID	CHEMISTRY
701,036	 Chemistry 472
701,037	 Chemistry 473
701,038	 Chemistry 474
701,039	 Chemistry 475
701,040	 Chemistry 476

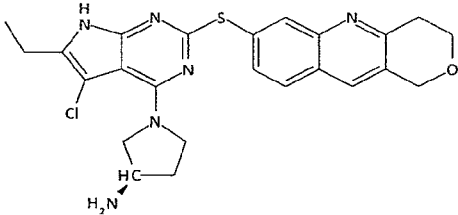
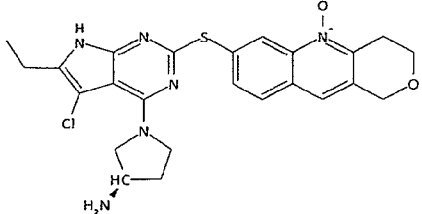
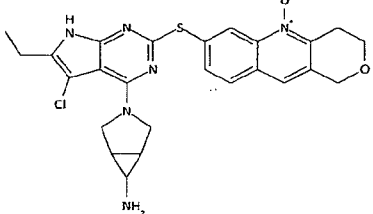
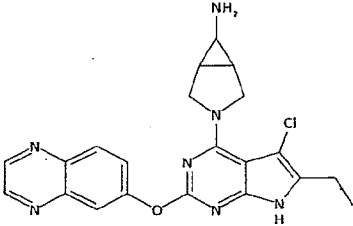
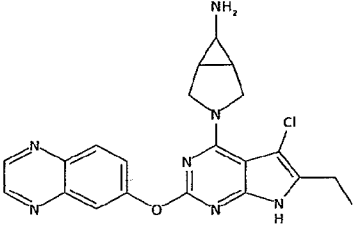
Rx ID	CHEMISTRY
701,041	 Chemistry 477
701,048	 Chemistry 478
701,049	 Chemistry 479
701,050	 Chemistry 480
701,051	 Chemistry 481

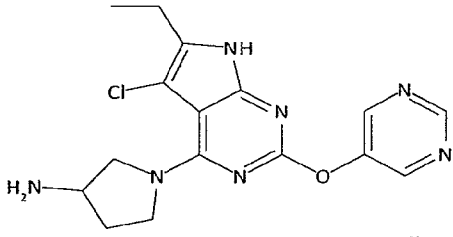
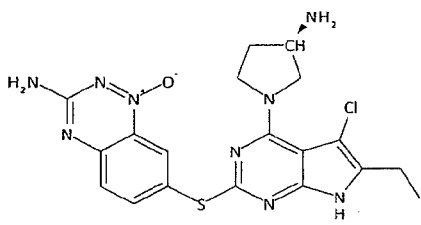
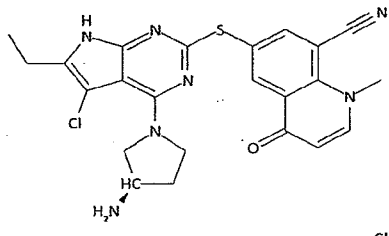
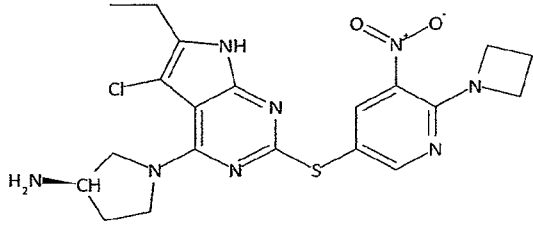
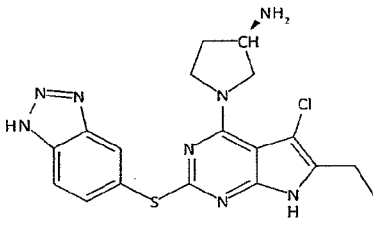
Rx ID	CHEMISTRY
701,053	 Chemistry 482
701,055	 Chemistry 483
701,057	 Chemistry 484
701,061	 Chemistry 485
701008-3	 Chemistry 486

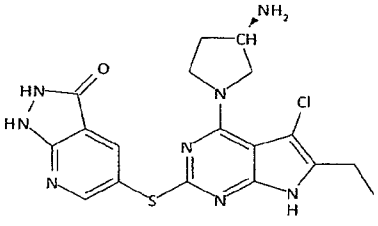
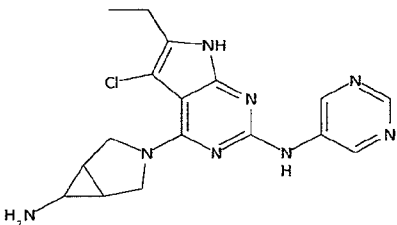
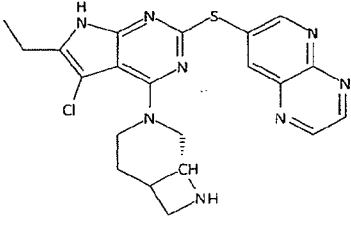
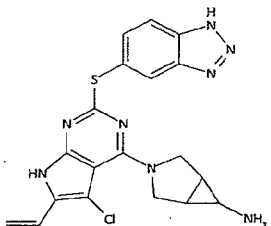
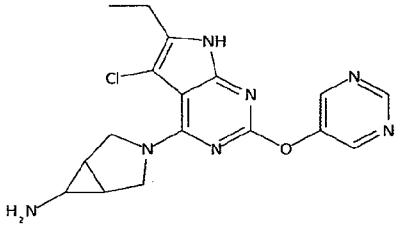
Rx ID	CHEMISTRY
701,062	 Chemistry 487
701,063	 Chemistry 488
701,064	 Chemistry 489
701,065	 Chemistry 490
701,066	 Chemistry 491

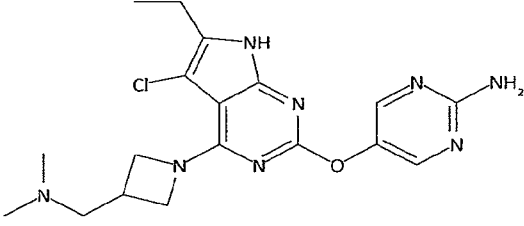
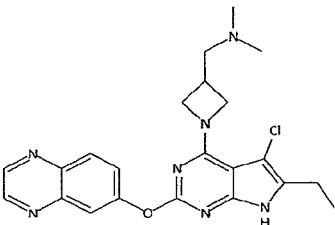
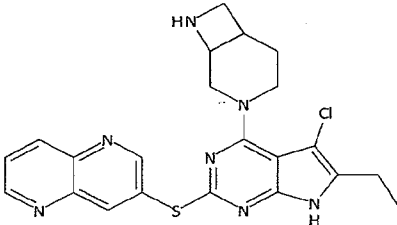
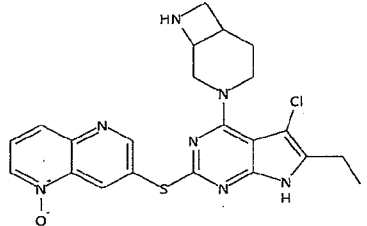
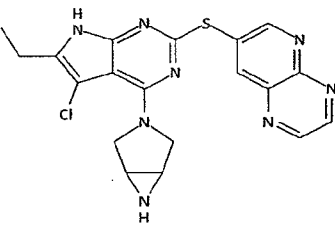
Rx ID	CHEMISTRY
701,067	 Chemistry 492
701,068	 Chemistry 493
701,069	 Chemistry 494
701008-3	 Chemistry 495
701,070	 Chemistry 496

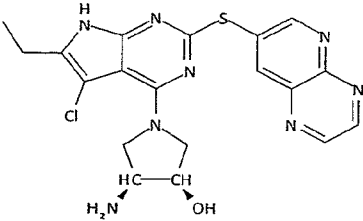
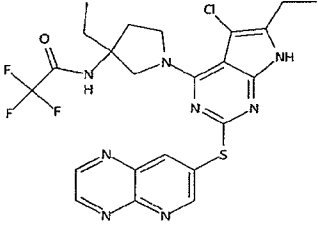
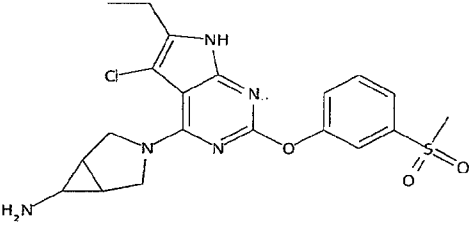
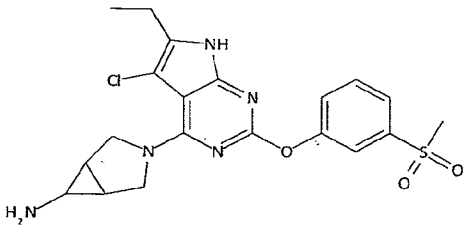
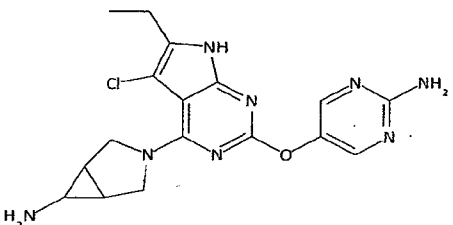
Rx ID	CHEMISTRY
701,071	 Chemistry 497
701,074	 Chemistry 498
701,075	 Chemistry 499
701,076	 Chemistry 500
701,080	 Chemistry 501

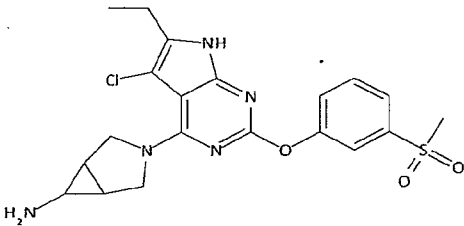
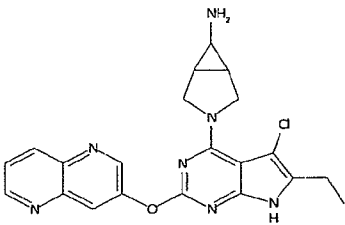
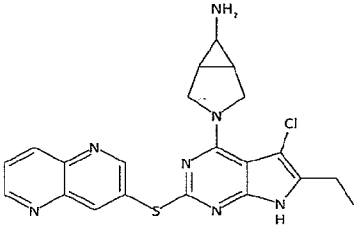
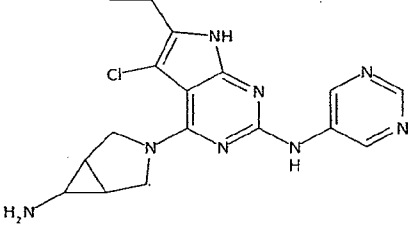
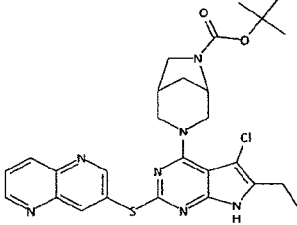
Rx ID	CHEMISTRY
701,082	 Chemistry 502
701,083	 Chemistry 503
701,084	 Chemistry 504
701,011	 Chemistry 505
701,011	 Chemistry 506

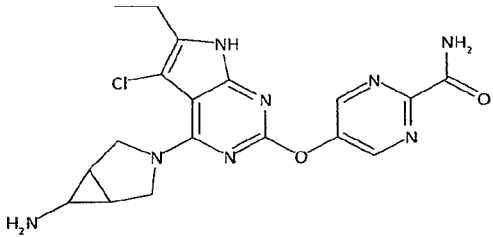
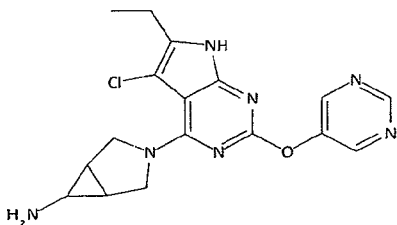
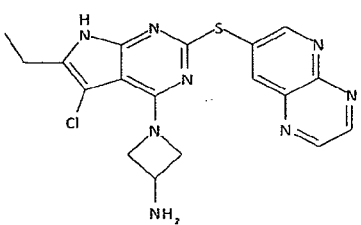
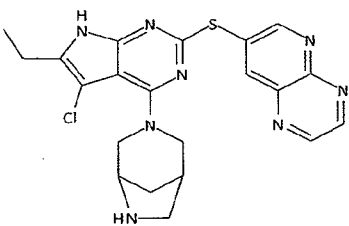
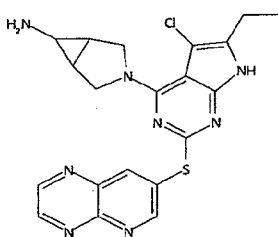
Rx ID	CHEMISTRY
701,071	 Chemistry 507
701,087	 Chemistry 508
701,088	 Chemistry 509
701,089	 Chemistry 510
701,090	 Chemistry 511

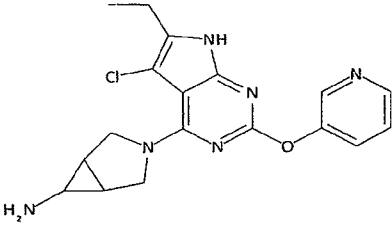
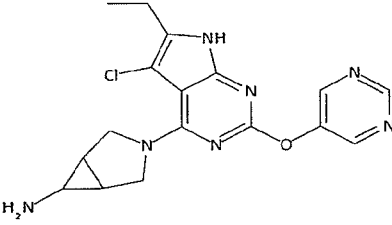
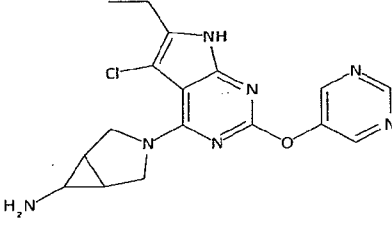
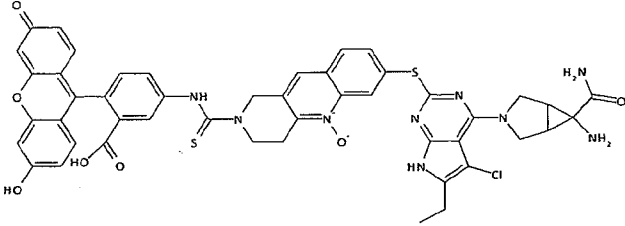
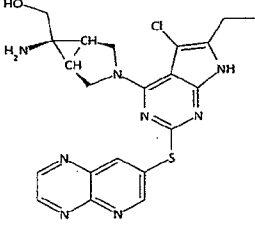
Rx ID	CHEMISTRY
701,094	 Chemistry 512
701,098	 Chemistry 513
701,102	 Chemistry 514
701,103	 Chemistry 515
701,080	 Chemistry 516

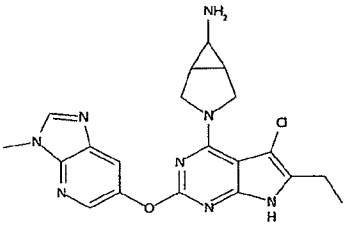
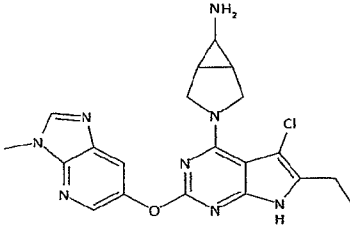
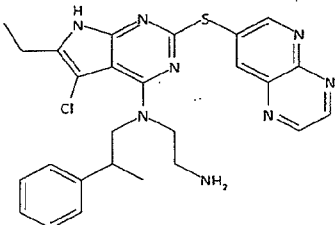
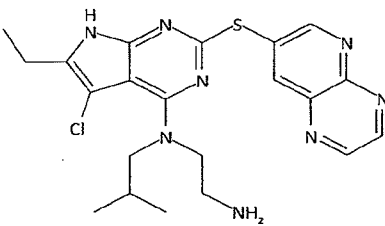
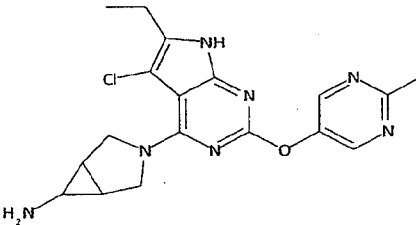
Rx ID	CHEMISTRY
701,112	 Chemistry 517
701,113	 Chemistry 518
701,115	 Chemistry 519
701,116	 Chemistry 520
701,118	 Chemistry 521

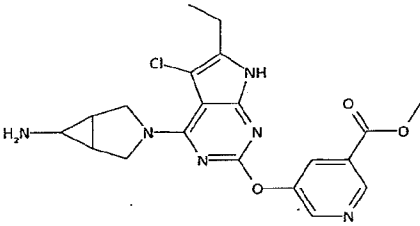
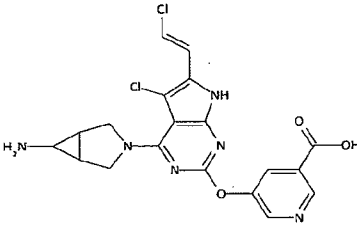
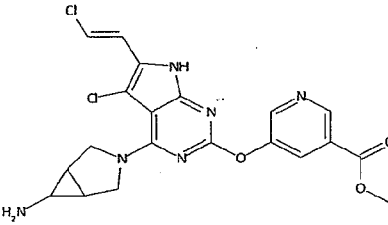
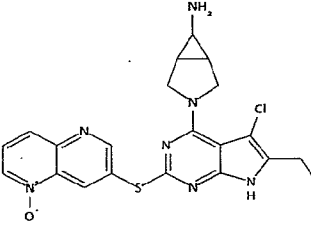
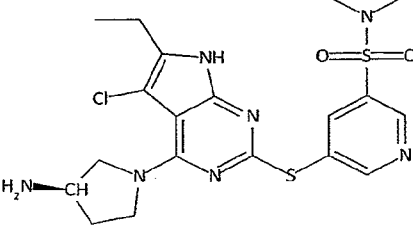
Rx ID	CHEMISTRY
701,119	 Chemistry 522
701,120	 Chemistry 523
701,121	 Chemistry 524
701,121	 Chemistry 525
701,122	 Chemistry 526

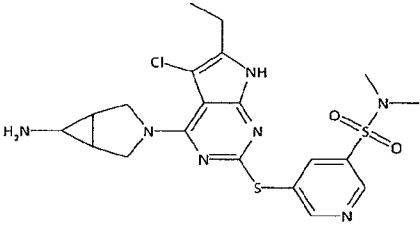
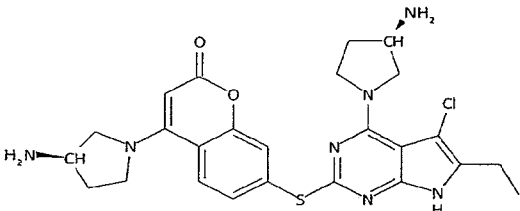
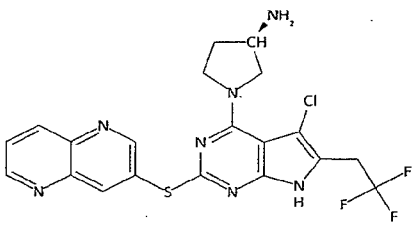
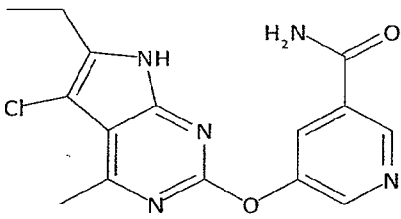
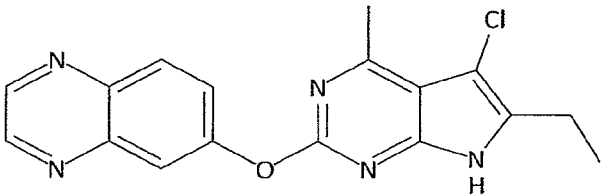
Rx ID	CHEMISTRY
701,121	 Chemistry 527
701,126	 Chemistry 528
700,800	 Chemistry 529
701,098	 Chemistry 530
701,132	 Chemistry 531

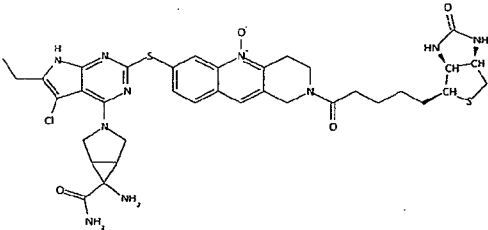
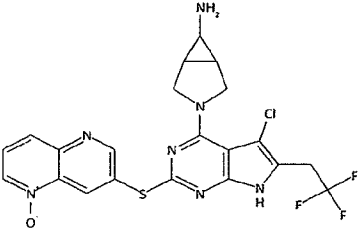
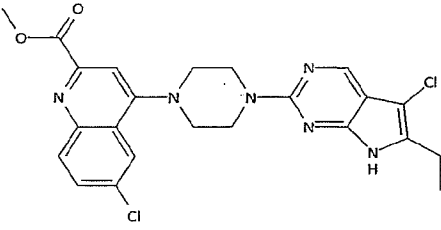
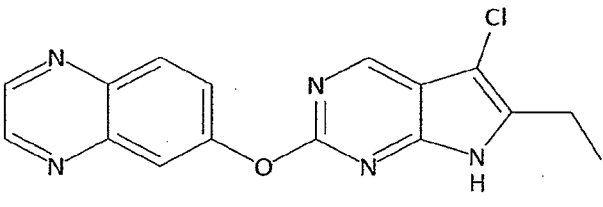
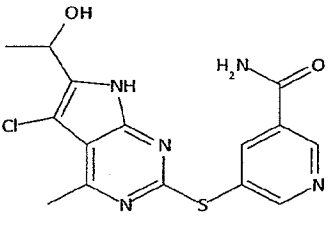
Rx ID	CHEMISTRY
701,133	 Chemistry 532
701,080	 Chemistry 533
700,434	 Chemistry 534
701,137	 Chemistry 535
700,609	 Chemistry 536

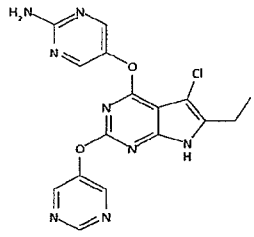
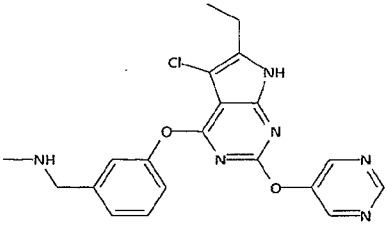
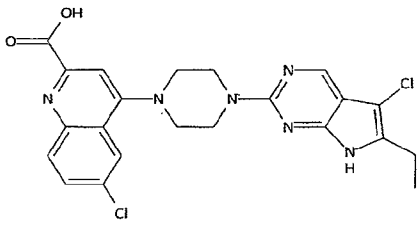
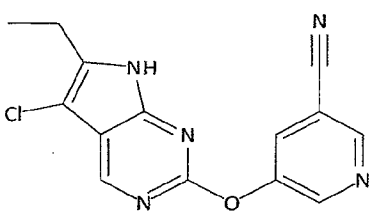
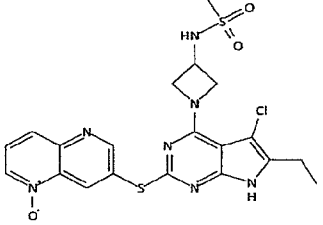
Rx ID	CHEMISTRY
701,140	 Chemistry 537
701,080	 Chemistry 538
701,080	 Chemistry 539
701,141	 Chemistry 540
701,144	 Chemistry 541

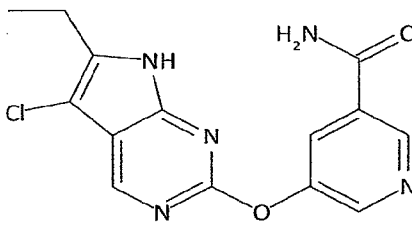
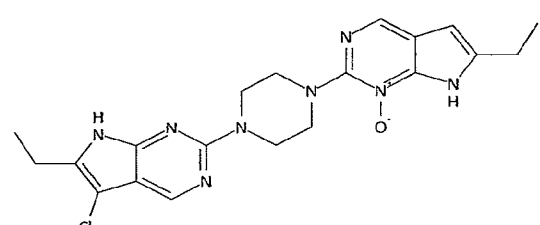
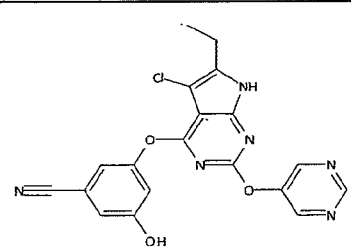
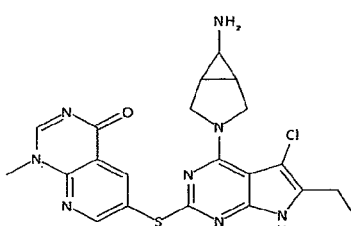
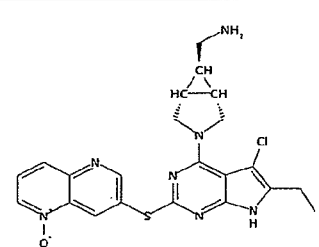
Rx ID	CHEMISTRY
701,107	 Chemistry 542
701,107	 Chemistry 543
701,147	 Chemistry 544
701,148	 Chemistry 545
701,151	 Chemistry 546

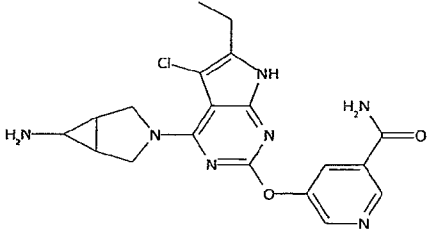
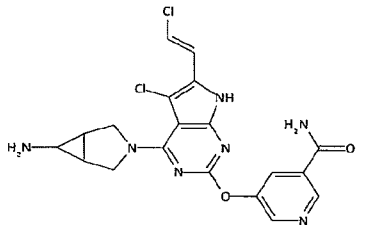
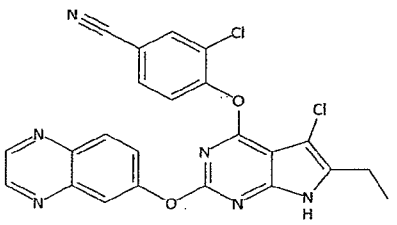
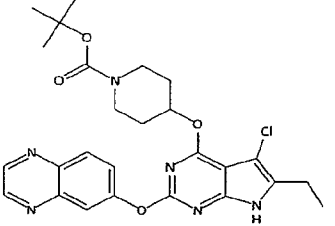
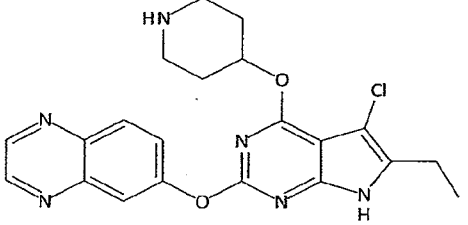
Rx ID	CHEMISTRY
701,163	 Chemistry 547
701,164	 Chemistry 548
701,165	 Chemistry 549
701,009	 Chemistry 550
701,180	 Chemistry 551

Rx ID	CHEMISTRY
701,181	 Chemistry 552
701,184	 Chemistry 553
701,209	 Chemistry 554
701,231	 Chemistry 555
701,232	 Chemistry 556

Rx ID	CHEMISTRY
701,229	 Chemistry 557
701,236	 Chemistry 558
701,237	 Chemistry 559
701,238	 Chemistry 560
701,240	 Chemistry 561

Rx ID	CHEMISTRY
701,241	 Chemistry 562
701,251	 Chemistry 563
701,260	 Chemistry 564
701,261	 Chemistry 565
701,263	 Chemistry 566

Rx ID	CHEMISTRY
701,265	 Chemistry 567
701,266	 Chemistry 568
701,264	 Chemistry 569
701,270	 Chemistry 570
701,269	 Chemistry 572

Rx ID	CHEMISTRY
701,278	 Chemistry 573
701,279	 Chemistry 574
701,286	 Chemistry 575
701,289	 Chemistry 576
701,290	 Chemistry 577

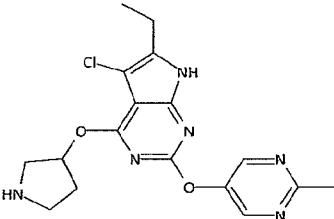
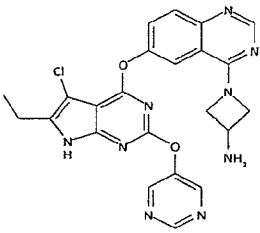
Rx ID	CHEMISTRY
701,291	 Chemistry 578
701,296	 Chemistry 579

Table 2

Rx_ID	SA	Spn52	EC8	Rx_ID	SA	Spn52	EC8
700,075	64			700,718	4	8	
700,076	>64			700,719	2	>64	
700,077	>64			700,720	8	16	
700,078	>64			700,721	32	32	
700,079	>64			700,722	4	8	
700,080	>64			700,723	<=0.5	2	
700,081	16			700,724	<=0.5	<=0.5	
700,082	>64			700,781	<=0.5	1	
700,084	>64			700,782	<=0.5	<=0.5	
700,085	>64			700,783	8	16	
700,088	>64			700,784	2	8	
700,089	>64			700,785	16	64	
700,090	>64			700,786	16	32	
700,091	>64			700,787	8	32	
700,092	64			700,788	8	16	
700,093	>64			700,789	2	8	
700,094	64			700,790	16	64	
700,095	>64			700,791	64	16	
700,096	>64			700,792	>64	>64	
700,098	>64			700,793	<=0.5	<=0.5	
700,099	>64			700,794	16	32	
700,100	>64			700,795	<=0.5	<=0.5	8
700,101	>64			700,796	<=0.5	1	
700,102	>64			700,797	>32	>32	
700,103	>64			700,798	16	32	
700,104	>64			700,799	>64	>64	
700,105	>64			700,800	<=0.5	<=0.5	
700,106	>64			700,800	<=0.5	<=0.5	
700,107	>64			700,801	<=0.5	<=0.5	
700,108	>64			700,802	4	16	
700,109	>64			700,803	8	16	
700,119	64			700,804	4	16	
700,120	4			700,805	<=0.5	2	
700,121	32			700,806	4	16	
700,122	>64			700,807	2	8	
700,127	>64			700,808	8	64	
700,128	>64			700,809	<=0.5	4	
700,129	16			700,812	4	4	
700,130	8			700,813	>64	>64	
700,131	64			700,814	2	4	
700,132	32			700,815	2	2	
700,133	>64			700,816	<=0.5	<=0.5	
700,135	>64			700,817	<=0.5	<=0.5	
700,136	16			700,818	2	8	
700,137	64			700,820	16	32	

Table 2

Rx_ID	SA	Spn52	EC8	Rx_ID	SA	Spn52	EC8
700,141	64			700,821	>64	>64	
700,142	32			700,822	>64	>64	
700,147	>64			700,823	64	64	
700,148	>64			700,824	2	8	
700,149	>64			700,825	64	>64	
700,150				700,826	8	32	
700,220	>64	64		700,827	4	32	
700,261	16	32		700,828	>64	>64	
700,267	2	16		700,829	16	32	
700,268	4	16		700,830	<=0.5	2	
700,269	4	16		700,831	2	4	
700,270	2	8		700,832	4	>8	
700,271	>64	>64		700,833	<=0.5	2	
700,273	4	16		700,834	1	8	
700,274	4	16		700,841	4	8	
700,275	1	8		700,842	4	>64	
700,281	32	64		700,843	64	>64	
700,282	<=0.5	4		700,844	64	32	
700,286	4	32		700,845	>64	>64	
700,287	>64	>64		700,846	>64	>64	
700,288	>64	64		700,847	>64	>64	
700,290	>64	>64		700,848	64	64	
700,291	>64	>64		700,850	64	>64	
700,292	>64	>64		700,851	<=0.5	4	
700,293	32	32		700,857	1	1	
700,294	>64	>64		700,858	8	>64	
700,295	>64	32		700,859	32	>64	
700,296	>64	64		700,860	>64	>64	
700,297	<=0.5	2		700,861	16	>64	
700,298	2	8		700,862	>64	32	
700,301	64	>64		700,863	8	8	
700,302	32	>64		700,864	4	4	
700,303	4	32		700,865	1	<=0.5	
700,304	8	32		700,866	1	8	
700,305	>64	>64		700,867	<=0.5	1	
700,306	>64	>64		700,868	>64	>64	
700,307	4	64		700,869	2	4	
700,315	16	64		700,870	64	64	
700,317	>64	>64		700,871	<=0.5	2	
700,318	>64	>64		700,872	1	2	
700,320	>64	>64		700,873	2	32	
700,321	64	64		700,874	2	8	
700,322	>64	>64		700,875	32	>32	
700,323	>64	>64		700,876	8	8	
700,324	>64	64		700,877	4	8	

Table 2

Rx_ID	SA	Spn52	EC8	Rx_ID	SA	Spn52	EC8
700,325	>64	>64		700,878	<=0.5	<=0.5	
700,326	>64	32		700,883	<=0.5	<=0.5	
700,327	32	64		700,884	4	16	
700,328	>64	64		700,885	2	4	
700,331	8	>64		700,886	>8	8	
700,332	>64	>64		700,887	8	4	
700,334	>64	>64		700,888	>64	>64	
700,338	8	64		700,889	32	32	
700,339	>64	>64		700,890	2	4	
700,340	>64	>64		700,891	>64	>64	
700,341	>64	>64		700,892	>64	>64	
700,342	>64	>64		700,893	4	8	
700,343	>64	>64		700,894	32	8	
700,345	<=0.5	2		700,898	<=0.5	2	
700,346	<=0.5	<=0.5		700,899	<=0.5	<=0.5	
700,347	1	8		700,900	8	8	
700,350	32	64		700,901	8	4	
700,351	>64	>64		700,903	32	64	
700,353	>64	>64		700,904	32	>64	
700,354	2	>64		700,906	2	4	>64
700,355	>64	>64		700,907	8	16	64
700,356	>64	>64		700,908	8	16	>64
700,357	>64	>64		700,909	1	4	>64
700,358	>64	>64		700,910	>64	>64	>64
700,359	2	8		700,911	1	2	>32
700,360	<=0.5	2		700,912	8	>64	32
700,361	>64	>64		700,913	2	2	>64
700,362	>64	>64		700,914	64	>64	32
700,363	>64	>64		700,915	64	>64	32
700,364	32	>64		700,916	64	>64	>64
700,365	>64	>64		700,917	4	4	8
700,373	>64	>64		700,918	2	8	>64
700,374	>64	>64		700,919	>64	>64	>64
700,378	>64	>64		700,920	>64	>64	>64
700,381	1	8		700,921	2	4	>64
700,385	8	>64		700,922	32	64	4
700,386	<=0.5	8		700,923	16	8	64
700,387	16	>64		700,924	16	4	64
700,388	4	16		700,925	4	32	>64
700,389	>64	>64		700,926	1	2	8
700,390	<=0.5	<=0.5		700,927	<=0.5	1	>64
700,391	>64	>64		700,928	2	8	16
700,392	<=0.5	<=0.5		700,929	16	64	32
700,393	<=0.5	1		700,930	8	16	>64
700,395	>64	>64		700,932	>64	>64	>64

Table 2

Rx_ID	SA	Spn52	EC8	Rx_ID	SA	Spn52	EC8
700,396	>64	>64		700,933	2	4	>64
700,397	>64	>64		700,934	4	16	>64
700,398	>64	>64		700,935	2	32	>64
700,402	>64	>64		700,936	64	32	>64
700,403	4	8		700,937	<=0.5	1	>64
700,404	<=0.5	<=0.5		700,938	<=0.5	<=0.5	>64
700,405	<=0.5	2		700,939	<=0.5	1	>64
700,406	2	16		700,940	2	8	8
700,407	>64	>64		700,941	4	8	>64
700,408	>64	>64		700,942	16	16	8
700,410	1	4		700,943	32	32	64
700,411	>64	>64		700,944	8	8	>64
700,412	>64	>64		700,945	<=0.5	<=0.5	>64
700,413	8, 1	8		700,946	>64	>64	>64
700,414	<=0.5	1		700,947	>64	64	>64
700,415	<=0.5	1		700,948	<=0.5	4	>16
700,416	<=0.5	2		700,949	<=0.5	4	>64
700,417	1	16		700,950	>64	>64	>64
700,418	1	8		700,951	>16	>16	>16
700,422	>64	>64		700,952	64	64	>64
700,423	1	2		700,953	>32	>32	>32
700,424	<=0.5	1		700,954	>32	>32	>32
700,425	<=0.5	2		700,955	8	>64	16
700,426	1	1		700,956	8	32	>64
700,427	<=0.5	1		700,957	<=0.5	1	>32
700,428	<=0.5	1		700,958	2	4	>32
700,429	<=0.5	2		700,959	2	2	>64
700,430	32	32		700,960	2	2	>32
700,431	>64	>64		700,961	1	1	>64
700,432	1	4		700,962	<=0.5	2	>8
700,433	<=0.5	1		700,963	1	4	>64
700,434	1	2		700,964	<=0.5	<=0.5	>64
700,434	1	2		700,965	<=0.5	<=0.5	64
700,435	<=0.5	1		700,966	<=0.5	<=0.5	>64
700,436	<=0.5	1		700,967	<=0.5	4	>64
700,437	<=0.5	2		700,968	2	>64	>64
700,438	<=0.5	1		700,969	<=0.5	2	>64
700,439	<=0.5	1		700,970	8	32	>64
700,440	<=0.5	<=0.5		700,971	<=0.5	2	>64
700,441	<=0.5	2		700,972	<=0.5	1	4
700,442	<=0.5	2		700,973	<=0.5	2	>64
700,443	>64	>64		700,974	<=0.5	2	32
700,444	4	8		700,975	8	8	>64
700,445	16	16		700,976	4	2	8
700,448	1	2		700,977	16	4	8

Table 2

Rx_ID	SA	Spn52	EC8	Rx_ID	SA	Spn52	EC8
700,449	1	1		700,978	>64	>64	>64
700,450	<=0.5	4		700,979	<=0.5	4	>64
700,451	1	4		700,980	<=0.5	2	>32
700,452	>64	>64		700,981	16	16	>32
700,453	<=0.5	<=0.5		700,982	<=0.5	<=0.5	>64
700,454	<=0.5	1		700,983	32	32	32
700,455	2	2		700,984	4	8	8
700,456	<=0.5	4		700,986	1	2	64
700,457	1	2		700,987	<=0.5	<=0.5	>64
700,458	2	8		700,988	<=0.5	<=0.5	>64
700,459	16	32		700,989	<=0.5	<=0.5	>64
700,461	1	>64		700,990	1	16	>64
700,462	>64	32		700,991	1	2	32
700,463	2	4		700,992	<=0.5	<=0.5	>64
700,464	>64	>64		700,993	<=0.5	2	16
700,465	8	32		700,994	<=0.5	<=0.5	8
700,466	4	16		700,995	>64	>64	64
700,467	4	16		700,996	<=0.5	<=0.5	>64
700,468	<=0.5	1		700,997	<=0.5	<=0.5	>64
700,469	1	2		700,998	<=0.5	1	>64
700,470	<=0.5	1		700,999	2	2	>64
700,471	2	8		701,000	4	8	64
700,472	64	64		701,000			
700,473	32	64		701,001	4	8	>64
700,474	8	8		701,002	4	>64	>64
700,475	>64	>64		701,003	>64	32	>64
700,476	>64	>64		701,004	32	>64	>64
700,477	1	16		701,005	<=0.5	<=0.5	16
700,478	64	>64		701,006	<=0.5	<=0.5	>64
700,479	4	32		701,007	<=0.5	2	>64
700,480	16	>64		701,010	<=0.5	1	>16
700,481	8	2		701,011	<=0.5	<=0.5	8
700,482	>64	>64		701,011	<=0.5	<=0.5	8
700,483	32	32		701,011	<=0.5	<=0.5	8
700,484	4	8		701,012	1	2	>64
700,485	4	>64		701,013	1	2	16
700,486	16	8		701,014	4	8	32
700,487	<=0.5	<=0.5		701,015	<=0.5	2	>64
700,490	>64	1		701,016	>64	>64	>64
700,491	<=0.5	1		701,017	2	1	>64
700,492	8	>64		701,018	>64	16	>64
700,493	>64	>64		701,019	>32	>32	>32
700,494	>64	>64		701,020	4	2	>64
700,495	64	>64		701,021	4	4	>64
700,496	>64	>64		701,022	4	2	>64

Table 2

Rx_ID	SA	Spn52	EC8	Rx_ID	SA	Spn52	EC8
700,497	1	4		701,023	>64	>64	>64
700,498	16	>64		701,024	2	2	>64
700,502	16	>64		701,025	<=0.5	2	16
700,503	16	>64		701,026	<=0.5	1	8
700,504	4	32		701,027	<=0.5	1	>64
700,505	4	32		701,028	<=0.5	<=0.5	>64
700,506	<=0.5	1		701,029	2	4	>64
700,507	>64	>64		701,030	<=0.5	<=0.5	>64
700,508	2	4		701,031	<=0.5	2	>64
700,509	16	16		701,032	8	8	>64
700,510	>64	>64		701,033	>64	>64	>64
700,511	>64	>64		701,034	4	4	>64
700,512	>64	>64		701,035	<=0.5	<=0.5	>64
700,513	>64	32		701,036	<=0.5	2	16
700,514	<=0.5	<=0.5		701,037	8	16	>64
700,515	1	1		701,038	8	32	16
700,516	<=0.5	1		701,039	8	8	>64
700,517	<=0.5	2		701,040	<=0.5	4	32
700,518	4	4		701,041	8	16	>32
700,519	1	1		701,042	<=0.5	1	>64
700,520	8	16		701,043	1	>64	>64
700,521	1	2		701,044	<=0.5	1	>64
700,522	<=0.5	2		701,045	<=0.5	1	>64
700,523	2	4		701,046	2	4	>64
700,524	<=0.5	<=0.5		701,047	<=0.5	<=0.5	>64
700,525	>64	>64		701,048	16	>64	>64
700,526	8	>64		701,049	<=0.5	<=0.5	8
700,527	16	8		701,050	<=0.5	<=0.5	32
700,528	8	8		701,051	2	4	>32
700,531	8	4		701,052	4	8	>16
700,534	2	>32		701,054	<=0.5	1	>64
700,535	<=0.5	4		701,055	>64	>64	>64
700,538	>16	>16		701,056	4	8	>64
700,539	<=0.5	1		701,057	8	32	>64
700,540	1	2		701,058	<=0.5	<=0.5	>32
700,541	4	4		701,059	<=0.5	<=0.5	>64
700,542	2	8		701,060	<=0.5	<=0.5	>64
700,544	>64	>64		701,061	<=0.5	<=0.5	>32
700,545	2	4		701,062	16	16	>64
700,546	4	16		701,063	2	2	4
700,547	4	4		701,064	8	4	4
700,548	<=0.5	2		701,065	8	4	16
700,549	4	4		701,066	4	>64	>64
700,550	1	8		701,067	>64	>64	>64
700,551	2	4		701,068	64	>64	>64

Table 2

Rx_ID	SA	Spn52	EC8	Rx_ID	SA	Spn52	EC8
700,552	<=0.5	2		701,069	<=0.5	<=0.5	8
700,558	8	>64		701,070	4	8	64
700,559	>64	>64		701,071	8	16	16
700,560	8	32		701,071	8	16	16
700,561	16	32		701,074	8	4	8
700,562	16	64		701,075	8	8	8
700,563	1	2		701,076	>64	64	>64
700,564	8	16		701,077	>64	>64	>64
700,565	2	4		701,080	1	2	4
700,566	>64	64		701,080	1	2	4
700,567	2	4		701,080	1	2	4
700,568	<=0.5	2		701,080	1	2	4
700,569	8	4		701,080	1	2	4
700,570	1	8		701,081	<=0.5	<=0.5	>32
700,571	8	8		701,082	<=0.5	16	4
700,572	4	>8		701,083	<=0.5	1	16
700,573	>64	>64		701,084	<=0.5	<=0.5	8
700,574	4	16		701,087	<=0.5	<=0.5	>64
700,575	8	16		701,088	1	1	32
700,576	8	16		701,089	2	4	>64
700,577	>64	>64		701,090	8	8	>64
700,578	<=0.5	1		701,091	<=0.5	<=0.5	>64
700,584	8	32		701,092	<=0.5	2	>64
700,585	>64	>64		701,093	<=0.5	4	>32
700,586	>64	>64		701,094	>64	>64	>64
700,587	64	>64		701,095	<=0.5	<=0.5	>64
700,588	8	8		701,096	<=0.5	<=0.5	>64
700,589	2	8		701,097	<=0.5	1	>64
700,590	4	16		701,098	4	4	32
700,591	2	>64		701,098	4	4	32
700,592	>64	4		701,102	<=0.5	1	16
700,595	8	8		701,104	<=0.5	<=0.5	>32
700,596	32	32		701,105	1	2	>64
700,597	16	16		701,106	2	4	>64
700,598	1	2		701,111	>64	16	>64
700,599	<=0.5	2		701,112	16	32	>64
700,600	>8	>8		701,113	32	32	>64
700,601	<=0.5	2		701,114	8	16	>64
700,602	4	4		701,115	<=0.5	<=0.5	16
700,603	4	8		701,116	<=0.5	2	16
700,604	4	8		701,117	8	8	>64
700,605	4	8		701,118	4	2	64
700,606	2	4		701,119	32	16	>64
700,607	8	16		701,120	4	32	>64
700,608	1	2		701,121	8	4	>64

Table 2

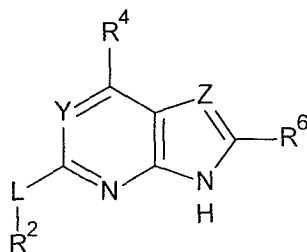
Rx_ID	SA	Spn52	EC8	Rx_ID	SA	Spn52	EC8
700,609	<=0.5	<=0.5		701,121	8	4	>64
700,609				701,121	8	4	>64
700,609	<=0.5	<=0.5		701,122	2	2	32
700,611	2	8		701,126	<=0.5	<=0.5	4
700,612	>64	>64		701,132	>64	>64	>64
700,613	<=0.5	4		701,133	8	8	>64
700,614	2	16		701,137	2	4	64
700,615	<=0.5	4		701,140	4	8	>64
700,618	<=0.5	2		701,143	<=0.5	2	64
700,619	32	32		701,144	<=0.5	2	32
700,620	32	>64		701,147	32	64	>64
700,621	4	8		701,148	64	64	>64
700,627	4	16		701,151	<=0.5	2	8
700,628	2	8		701,153	64	>64	>64
700,629	<=0.5	2		701,156	<=0.5	2	16
700,630	4	8		701,157	1	8	64
700,648	<=0.5	2		701,161	4	16	64
700,649	<=0.5	2		701,162	16	32	>32
700,650	<=0.5	1		701,163	>64	>64	>64
700,654	>64	>64		701,180	16	32	>64
700,655	>64	2		701,181	2	8	>64
700,656	<=0.5	2		701,182	>64	>64	>64
700,657	8	2		701,183	16	64	>64
700,658	<=0.5	8		701,184	>64	>64	>64
700,659	4	2		701,193	8	32	64
700,660	<=0.5	1		701,209	2	4	>64
700,661	>64	>64		701,229	4	32	>64
700,664	2	4		701,231	2	4	>64
700,665	2	8		701,232	1	4	>64
700,666	2	4		701,233	1	8	>64
700,667	<=0.5	1		701,236	>64	>64	>64
700,668	8	>64		701,237	>64	>64	>64
700,669	>64	>64		701,238	4	32	>64
700,670	16	16		701,239	2	16	64
700,671	8	32		701,240	>64	>64	>64
700,672	8	8		701,241	1	2	>64
700,673	2	4		701,249	<=0.5	<=0.5	8
700,676	4	8		701,250	<=0.5	<=0.5	>64
700,677	2	8		701,251	1	2	>64
700,678	1	2		701,252	<=0.5	<=0.5	>64
700,679	>64	>64		701,253	1	4	>64
700,680	16	64		701,254	<=0.5	<=0.5	>64
700,686	>64	>64		701,255	<=0.5	<=0.5	>64
700,687	>64	>64		701,260	8	64	>64
700,688	<=0.5	<=0.5		701,261	4	16	>64

Table 2

Rx_ID	SA	Spn52	EC8	Rx_ID	SA	Spn52	EC8
700,689	2	8		701,263	<=0.5	1	>64
700,690	>64	8		701,264	<=0.5	<=0.5	>64
700,691	>64	>64		701,265	4	16	>64
700,694	2	8		701,267	<=0.5	<=0.5	32
700,695	16	32		701,268	<=0.5	<=0.5	4
700,696	>64	16		701,269	<=0.5	<=0.5	8
700,697	4	8		701,270	<=0.5	4	32
700,698	<=0.5	8		701,273	<=0.5	<=0.5	16
700,699	2	64		701,278	>64	>64	>64
700,700	4	8		701,286	>64	>64	>64
700,701	1	8		701,287	>64	>64	>64
700,702	2	16		701,288	<=0.5	1	>64
700,705	>64	>64		701,289	16	>64	>64
700,706	1	2		701,290	>64	64	>64
700,707	2	4		701,291	32	16	64
700,708	32	>64		701,292	32	>32	>32
700,710	1	8		701,296	8	32	>64
700,711	1	8		701,297	4	16	>64
700,712	8	>64		701,298	2	4	>64
700,713	1	2		701,299	2	4	>64
700,714	2	4		701008-2	<=0.5	1	4
700,715	<=0.5	1		701009-2	<=0.5	<=0.5	2
700,716	1	2		701249-2	<=0.5	<=0.5	4
700,717	2	4					

WHAT IS CLAIMED IS:

1. A compound having the structure of Formula I



wherein

Y is N or CH;

Z is N or CR⁵;

R⁵ is H, a substituted or unsubstituted hydrocarbyl residue (1-3C) containing 0-2 heteroatoms selected from O, S and N, or is an inorganic residue;

L is O, S, NR⁷, or CR⁸R⁹;

R⁷ is H or C₁₋₃ alkyl;

R⁸ and R⁹ are each independently H or C₁₋₃ alkyl;

R² is H, a hydrocarbyl residue (1-40C) containing 0-10 heteroatoms selected from O, S and N optionally substituted with an inorganic residue;

R⁴ is H, an inorganic residue, or a hydrocarbyl residue (1-30C) containing 0-12 heteroatoms selected from O, S and N and containing 0-10 inorganic residues, wherein R⁵ and R⁴ together may join to form a fused ring; and

R⁶ is selected from the group consisting of H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, halo C₁₋₅ alkyl, halo C₂₋₅ alkenyl, halo C₂₋₅ alkynyl, C₁₋₅ hydroxyalkyl, C₁₋₅ alkyl chloride, C₂₋₅ alkenyl chloride, and C₂₋₅ alkynyl chloride;

or a pharmaceutically-acceptable salt, ester, or prodrug thereof.

2. The compound of claim 1, wherein

Y is N; and

L is O, S, NH, or CH₂.

3. The compound of claim 1 or 2, wherein Z is CR⁵, wherein R⁵ is selected from the group consisting of hydrogen, halo, unsubstituted C₁₋₃ alkyl, or C₁₋₃ alkyl substituted with

one or more substituents selected from the group consisting of =O, halo, NH₂, NHCH₃, and $\equiv$ N, or C₂₋₃ alkenyl, wherein R⁵ and R⁴ together may join to form a fused ring.

4. The compound of any of claims 1-3, wherein R⁵ is methyl, C(O)CH₃, C(O)NH₂, CH₂OH, CF₃, CN, CHF₂, CHO, acetyl, Cl or Br.

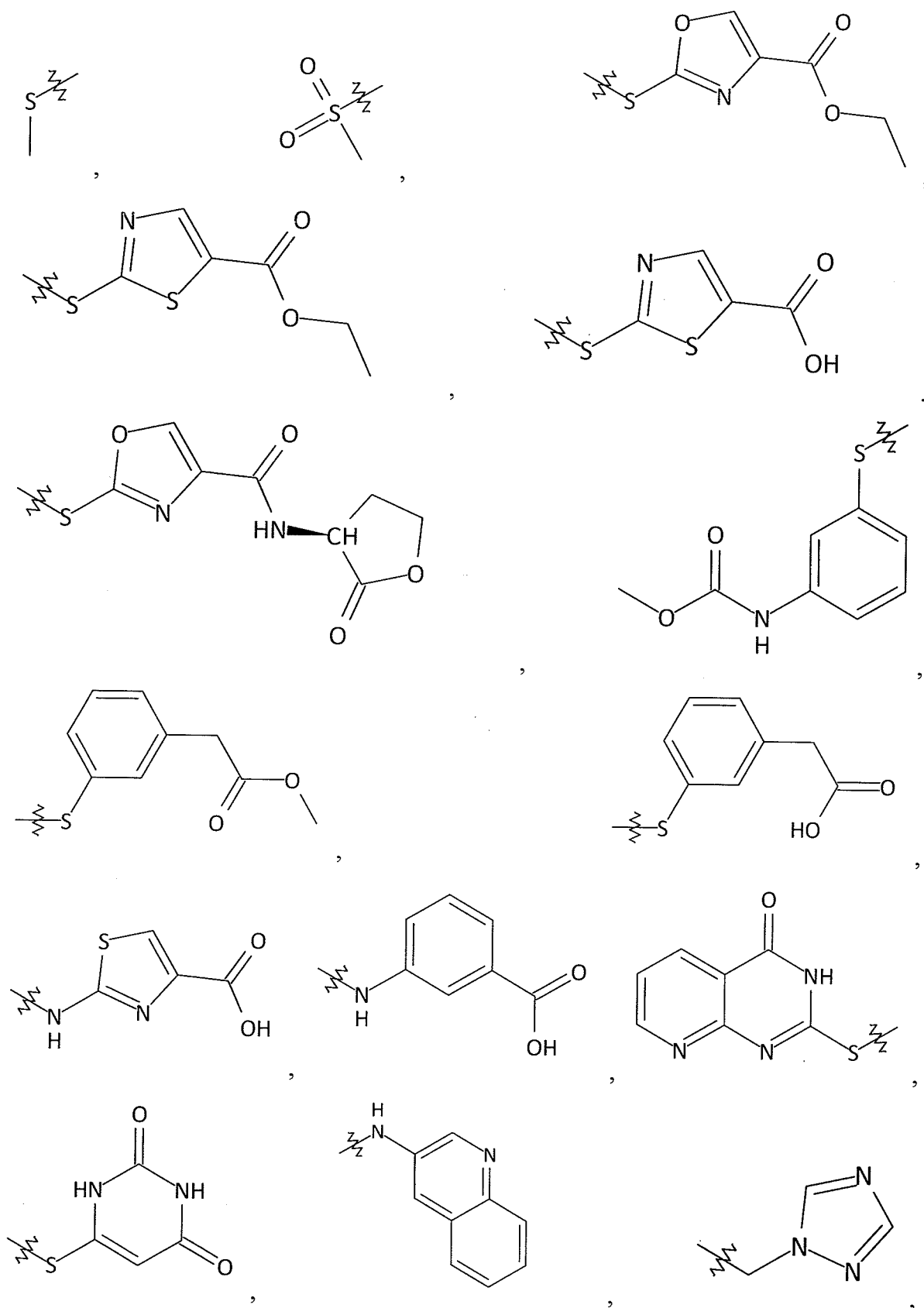
5. The compound of any of claims 1-4, wherein R² comprises at least one aryl or heteroaryl moiety.

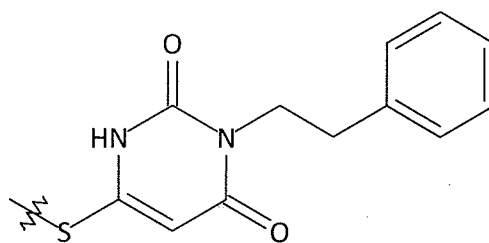
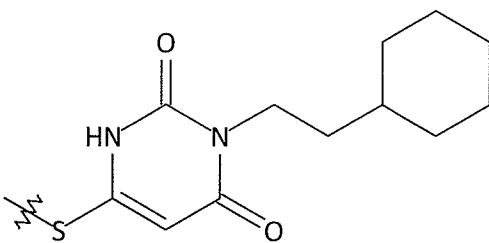
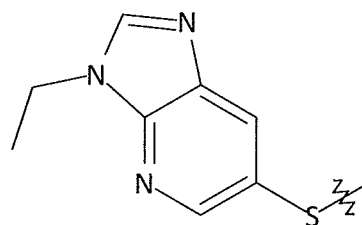
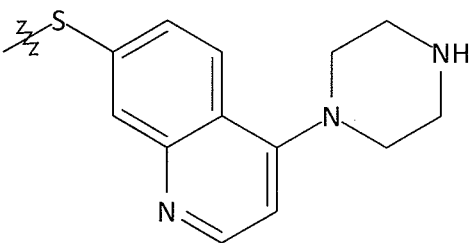
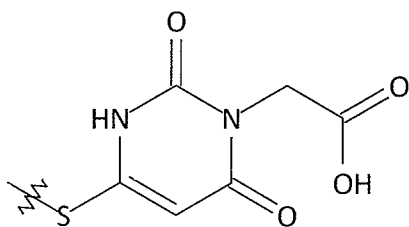
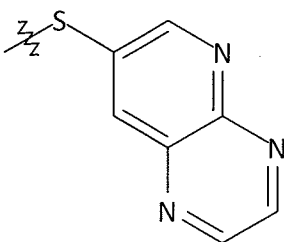
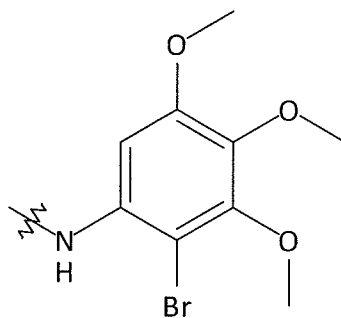
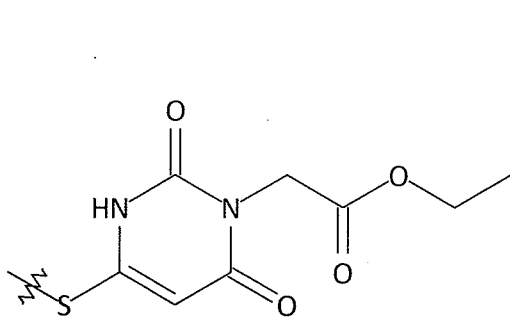
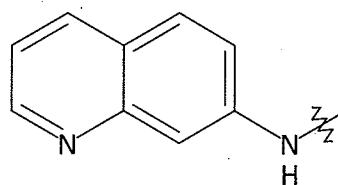
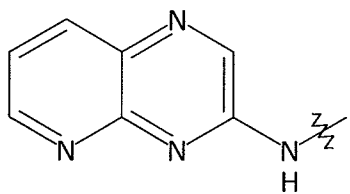
6. The compound of any of claims 1-5, wherein the at least one aryl or a heteraryl moiety of R² is directly linked to L.

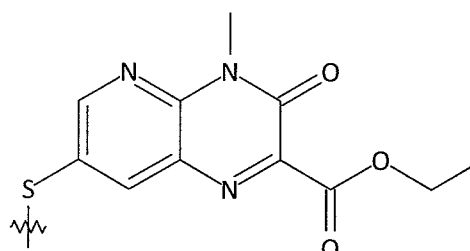
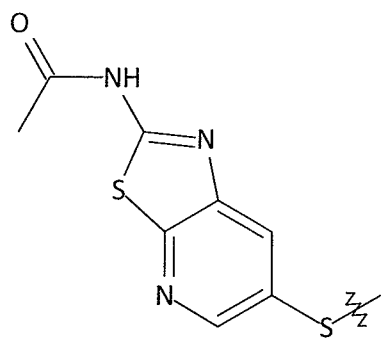
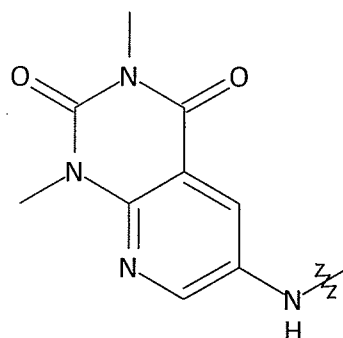
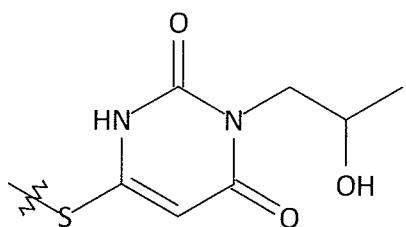
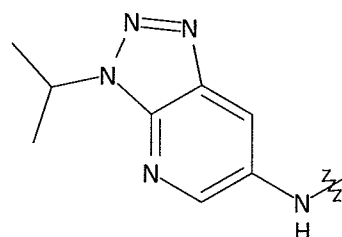
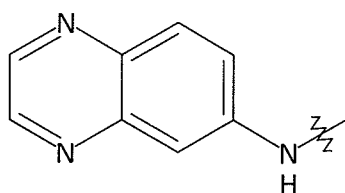
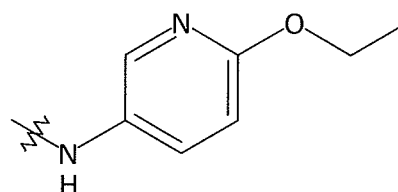
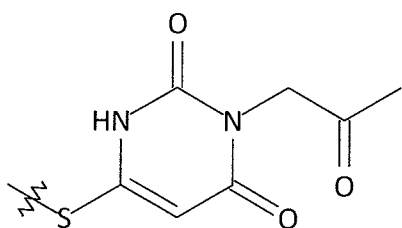
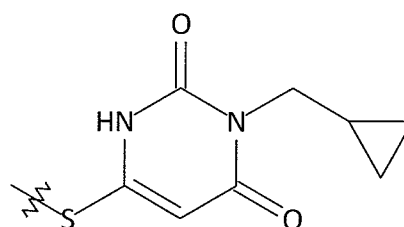
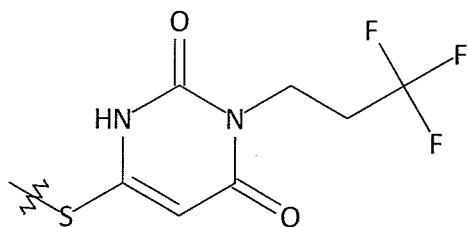
7. The compound of any of claims 1-6, wherein the at least one aryl or heteraryl moiety of R² is substituted with 0-4 alkyl, alkenyl, alkynyl, acyl, heteroaryl, heteroalkyl, haloalkyl, halo, O⁻ (if R² contains N), OR, NR₂, SR, SOR, SO₂R, OCOR, CONROR, NRCOR, NRCONR₂, NRCOOR, OCONR₂, COOR, SO₃R, CONR₂, CONR₂OR, SO₂NR₂, NRSO₂NR₂, CN, CF₃, or NO₂, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-14 members.

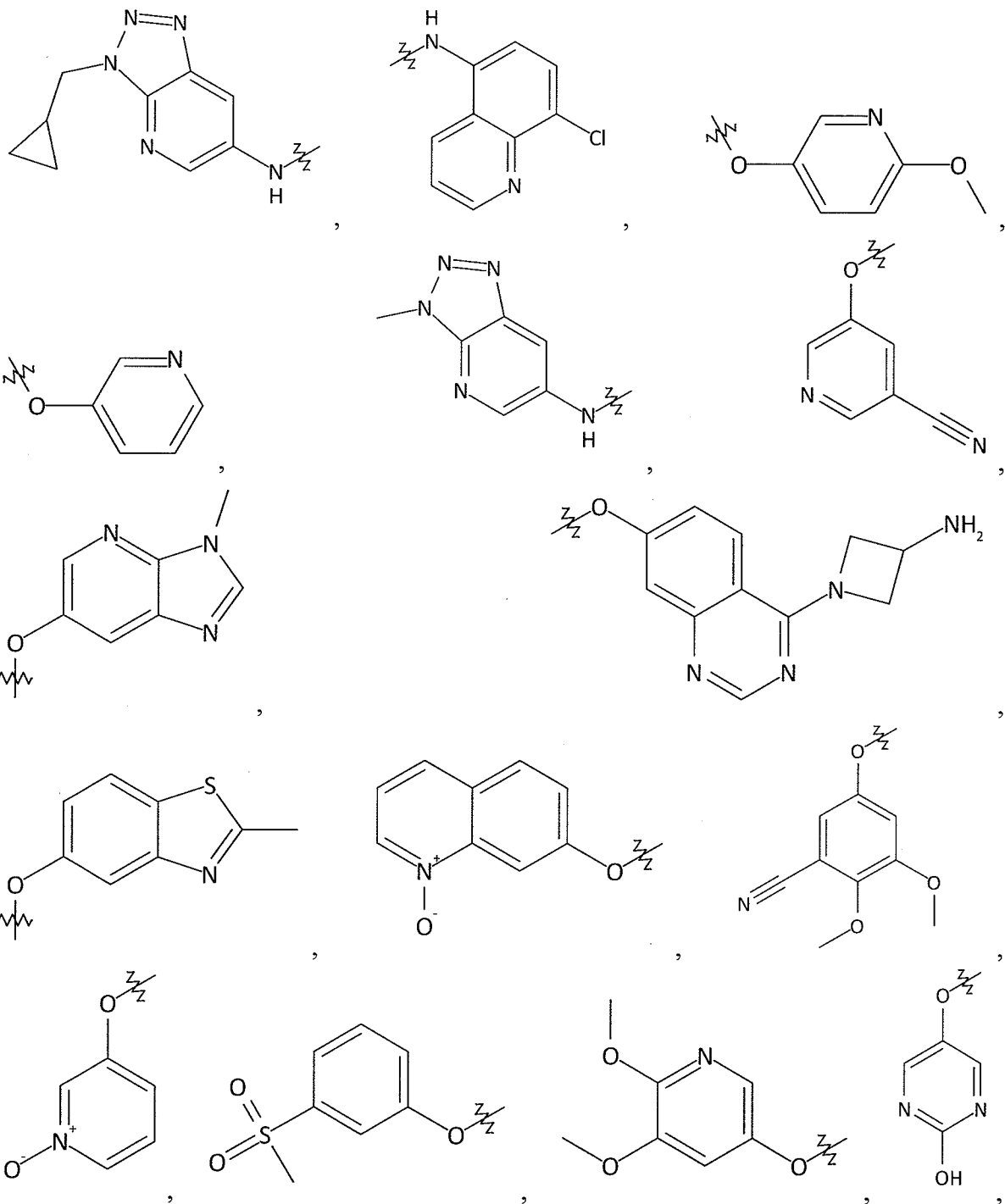
8. The compound of any of claims 1-7, wherein the aryl or heteroaryl moiety of R² comprises at least one moiety selected from the group consisting of phenyl, pyrido[2,3-b]pyrazine, pyridyl, thiazole, quinoline, pyridazine, pyrimidinedione, pyrido[2,3-d]pyrimidinedione, pyrimidine, [1,2,3]triazolo[4,5-b]pyridine, oxazole, benzotriazine, furo[3,2-b]pyridine, thiazolo[5,4-b]pyridine, pyrazolo[3,4-b]pyridine, imidazo[4,5-b]pyridine, pyrido[3,2-d]pyrimidine, 1,5-naphthyridine, quinolone, quinazoline, and quinoxaline.

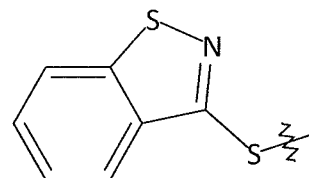
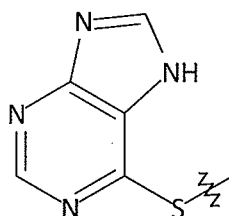
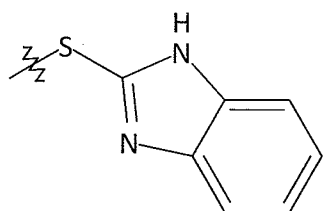
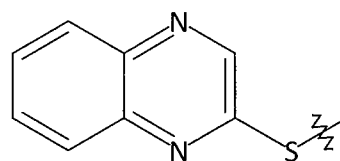
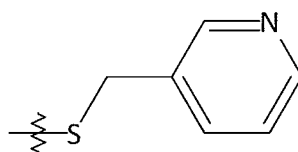
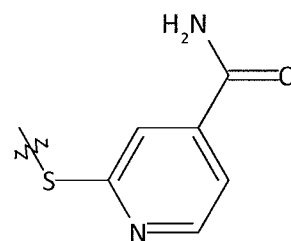
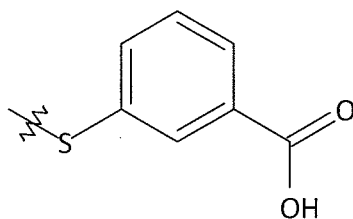
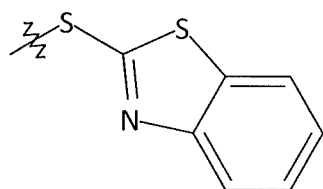
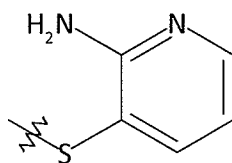
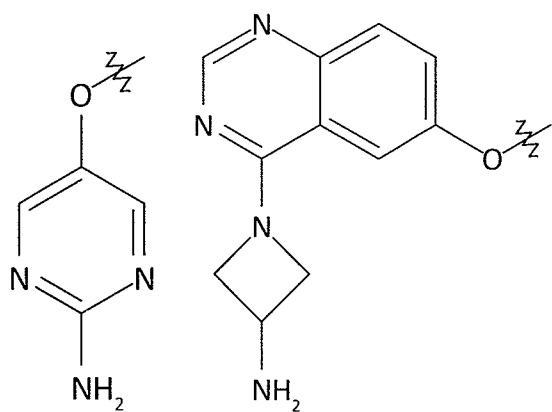
9. The compound of any of claims 1-8, wherein L-R² is selected from the group consisting of

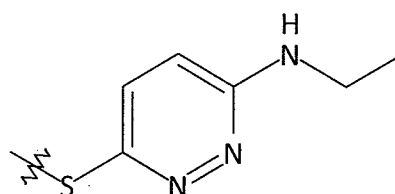
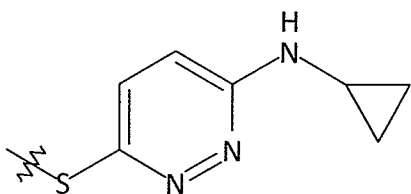
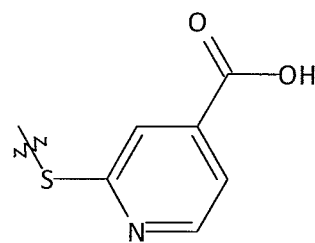
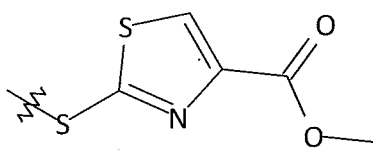
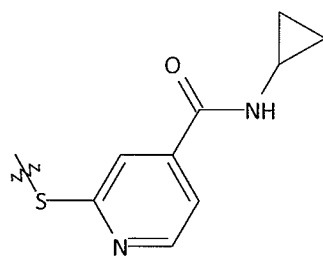
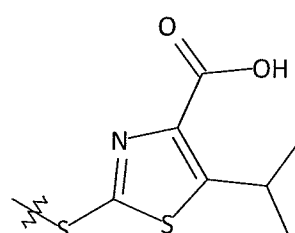
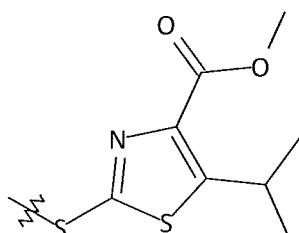
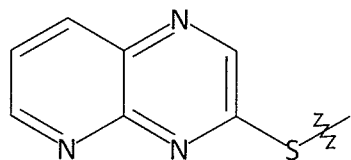
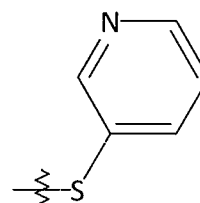
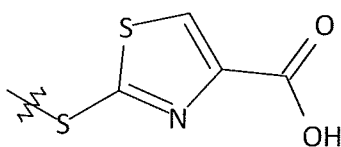
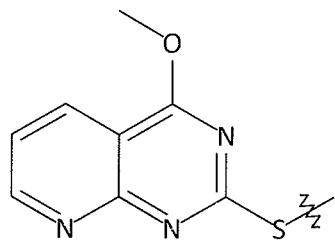
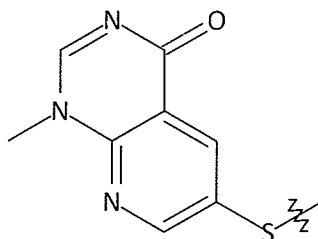
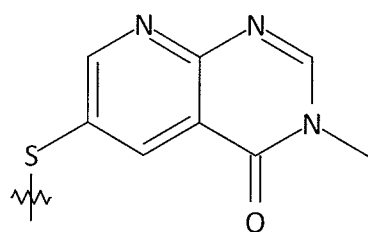
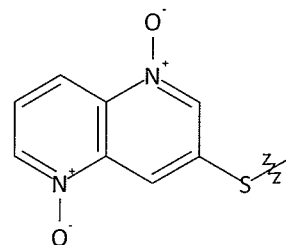
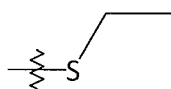
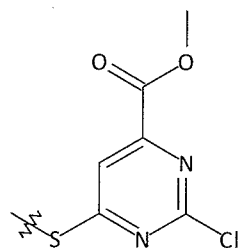


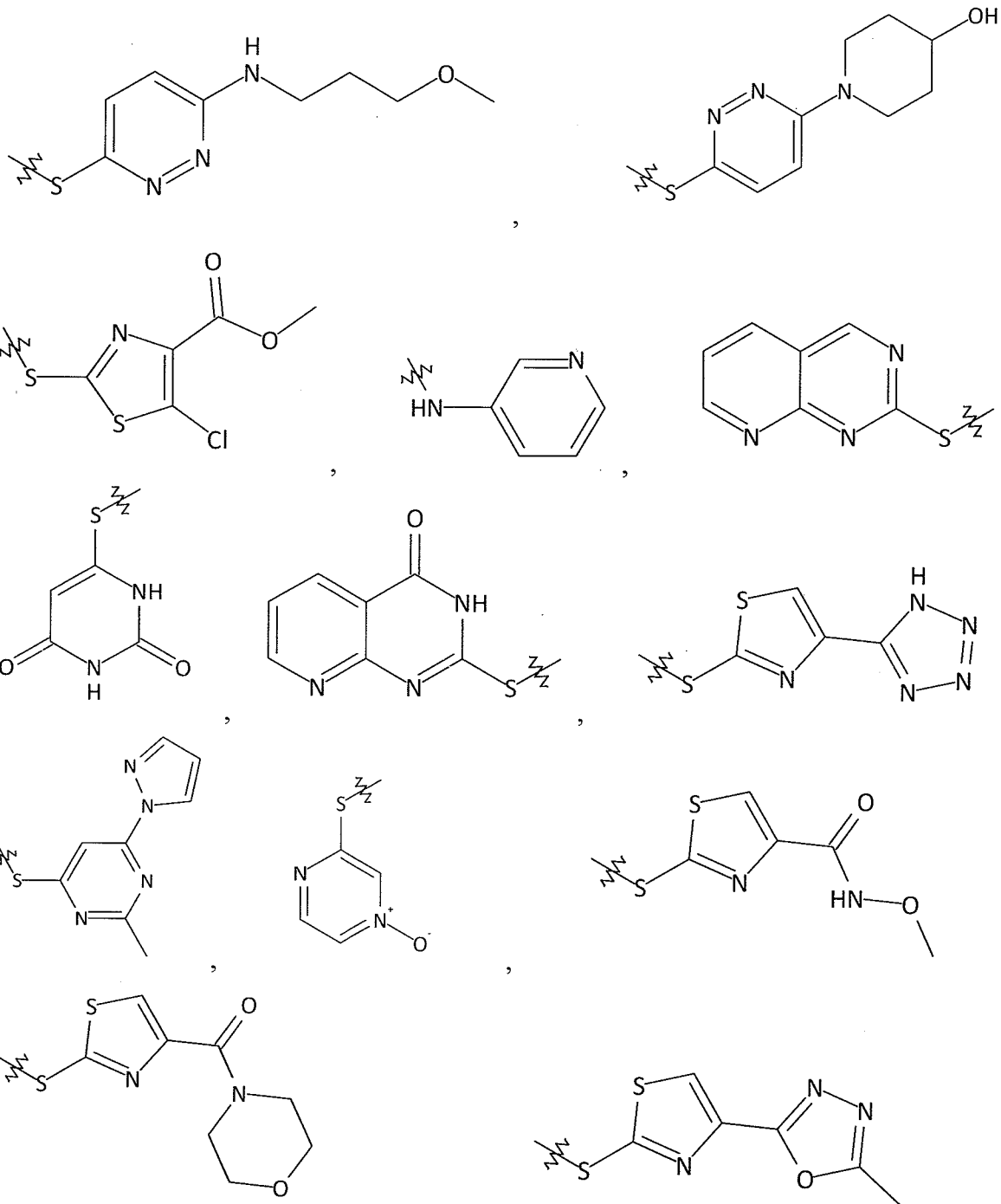


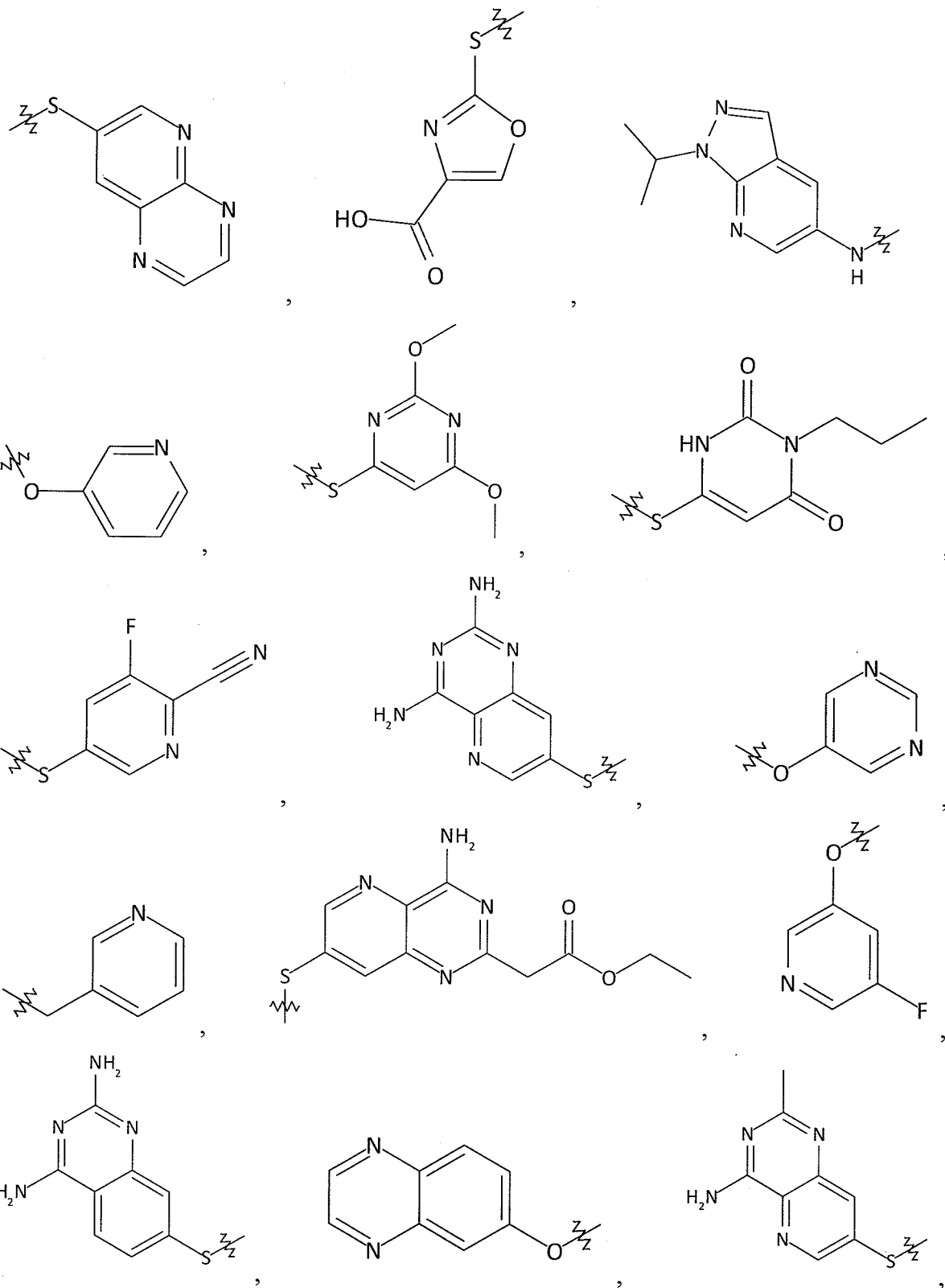


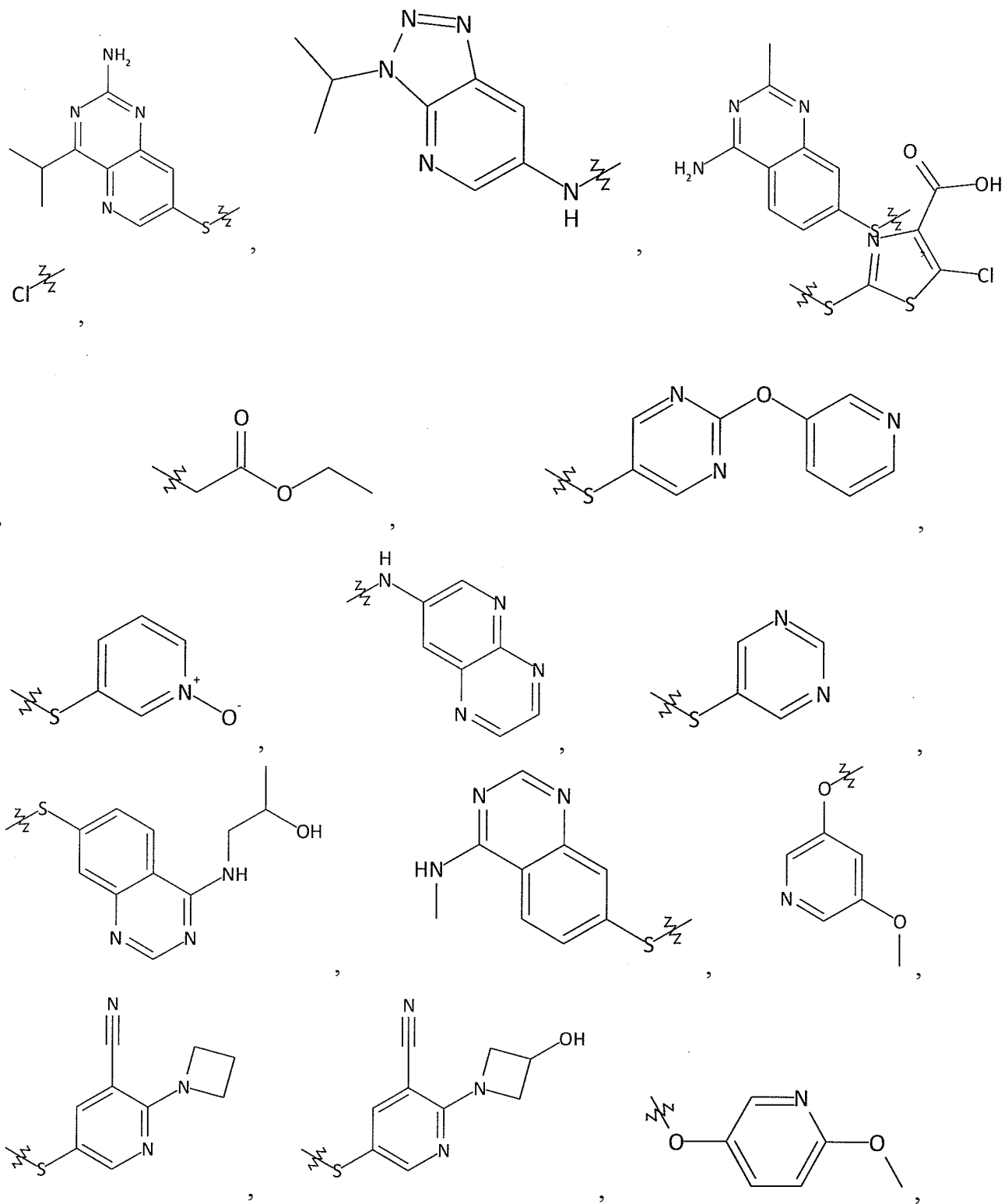


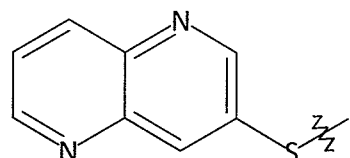
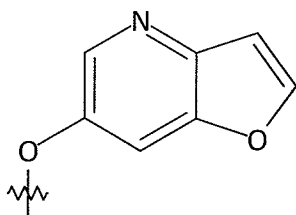
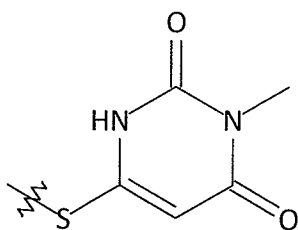
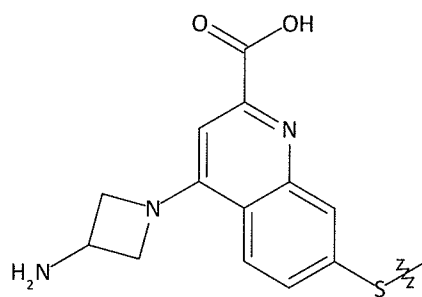
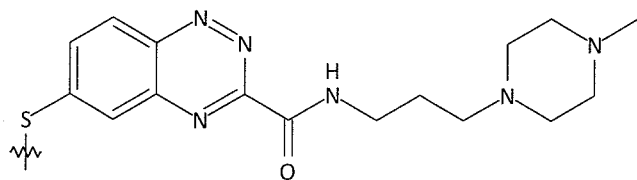
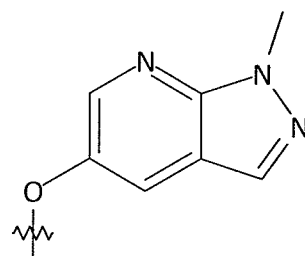
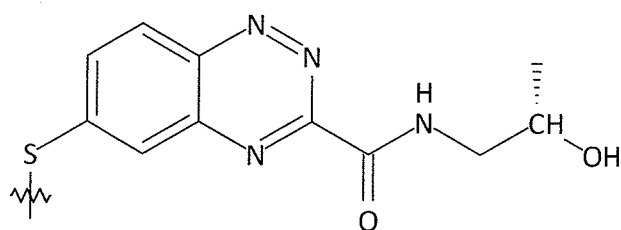
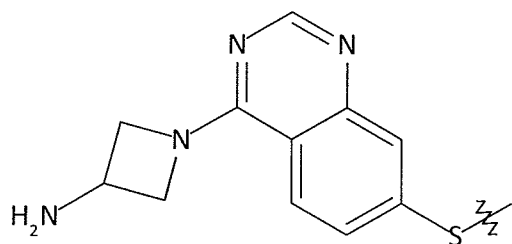
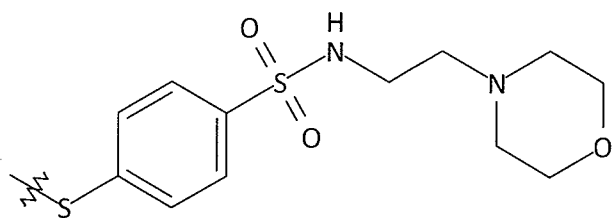


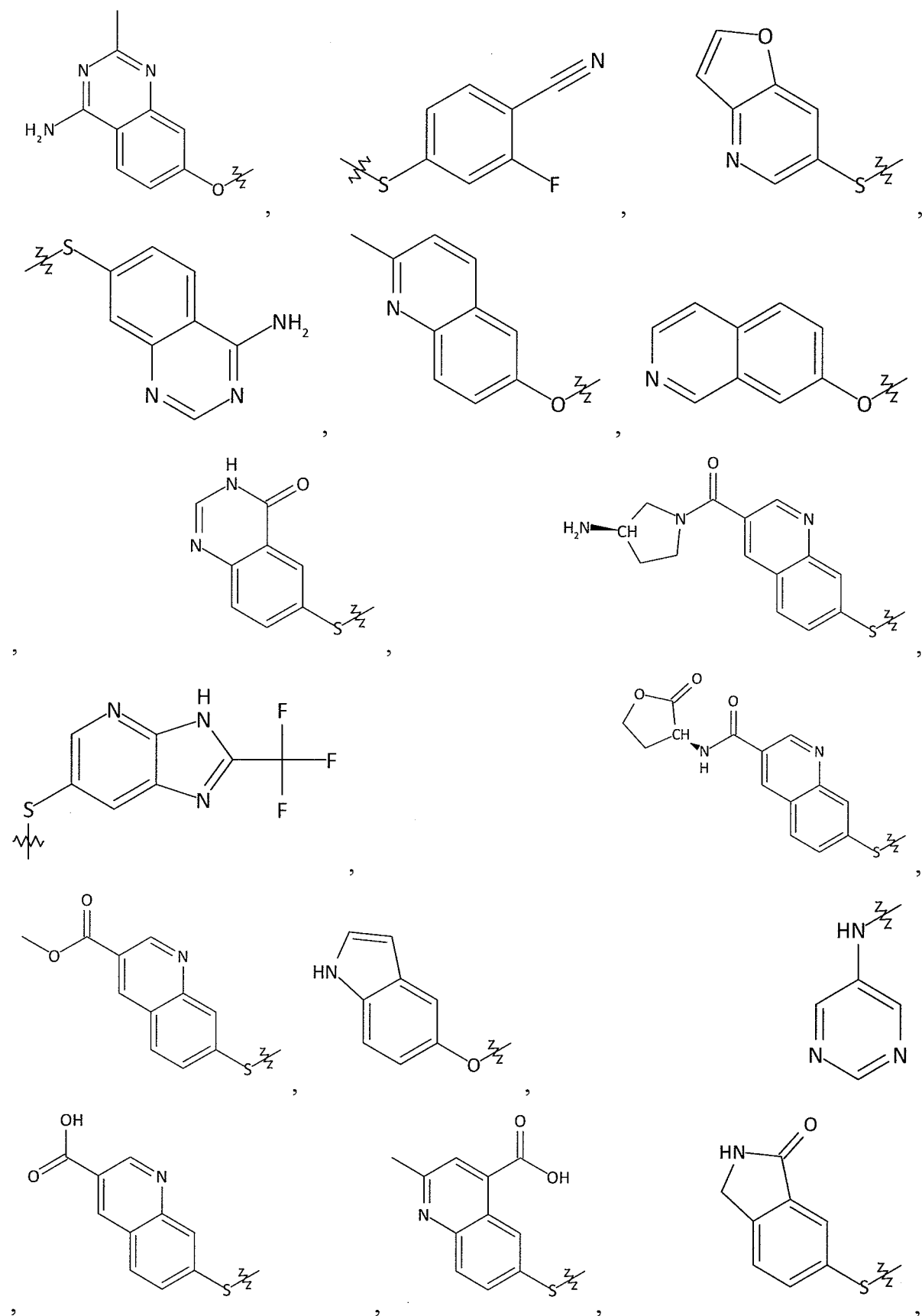


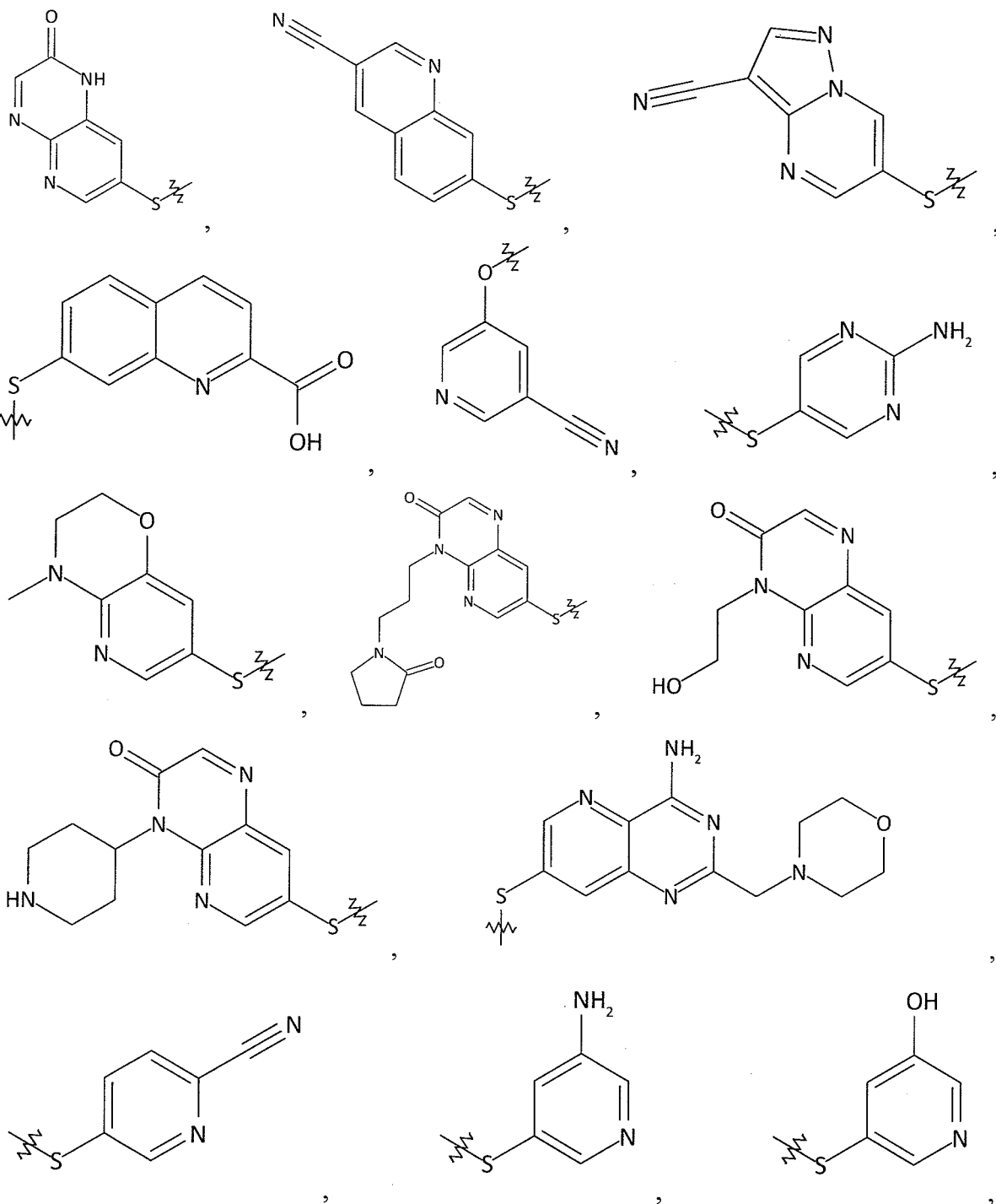


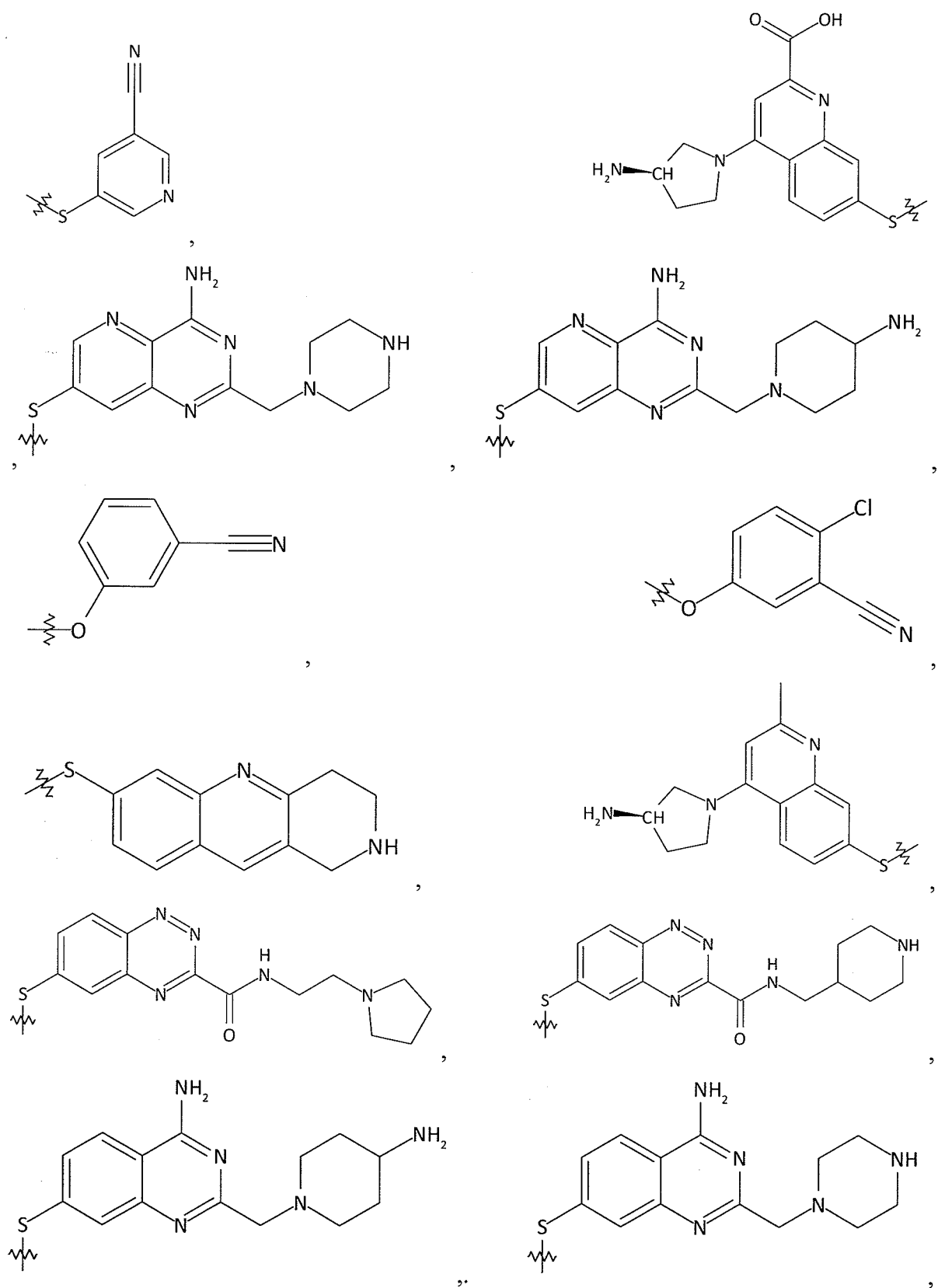


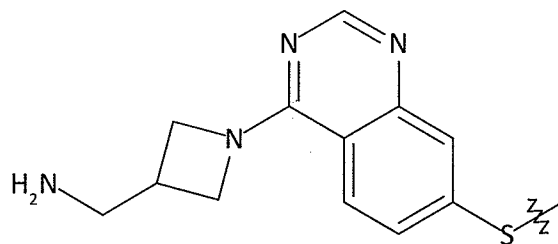
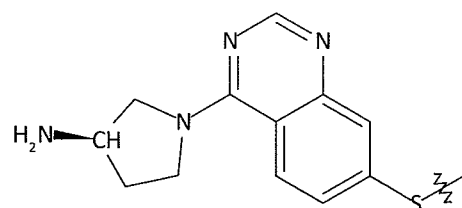
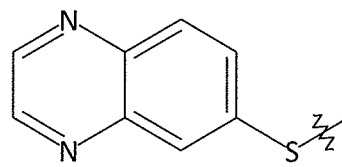
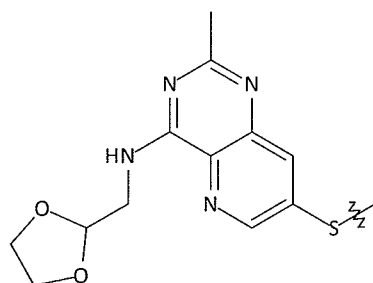
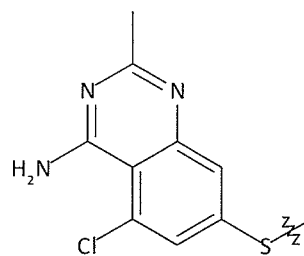
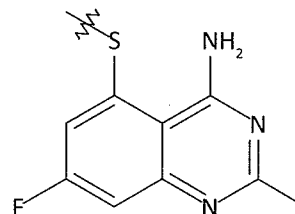
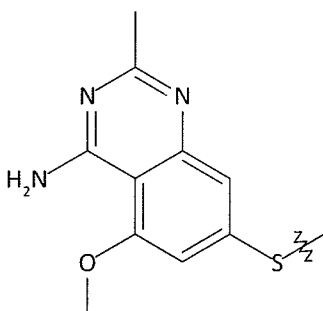
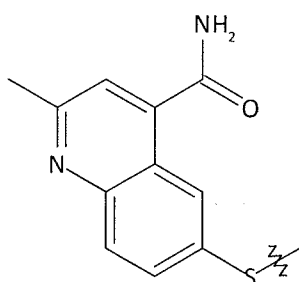
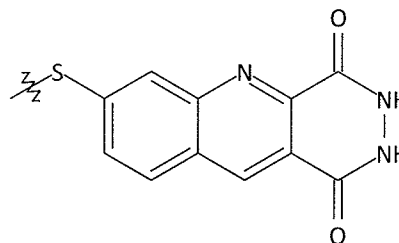
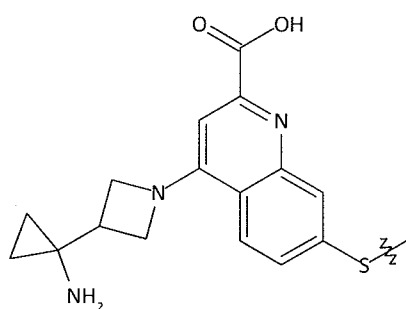
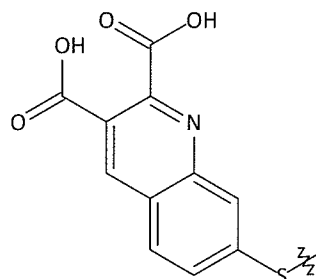
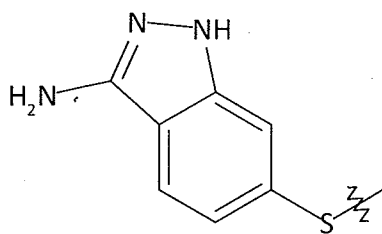
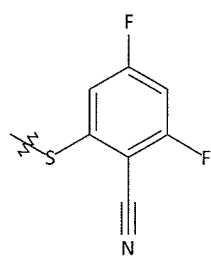


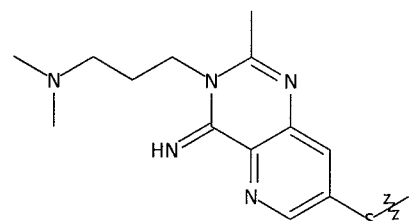
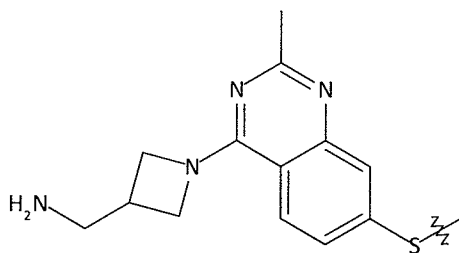
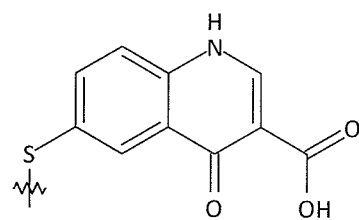
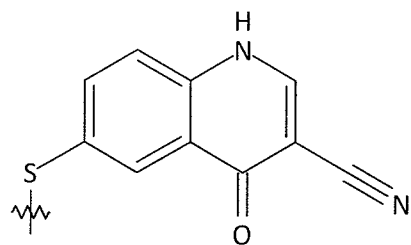
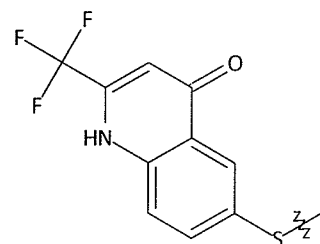
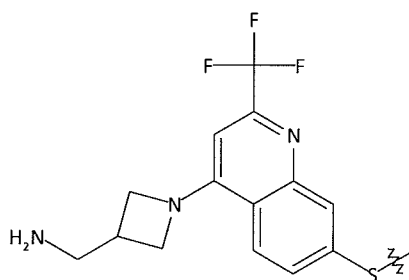
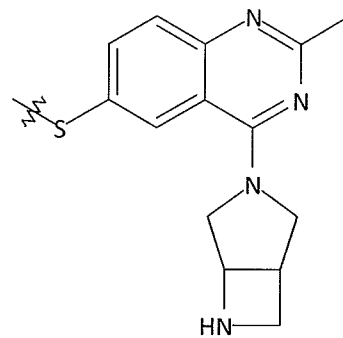
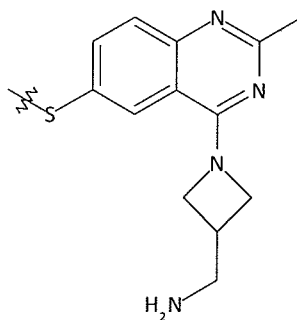
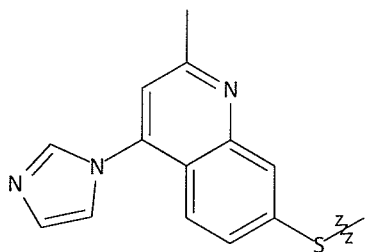
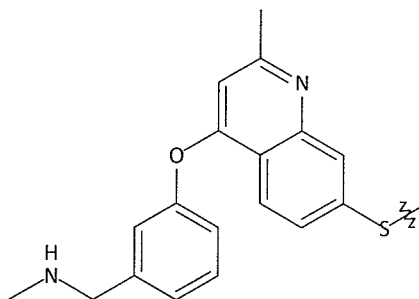
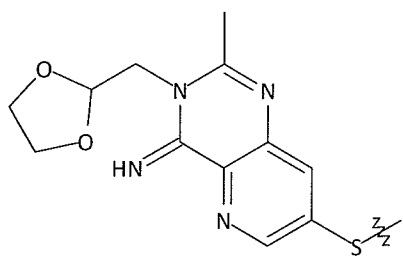


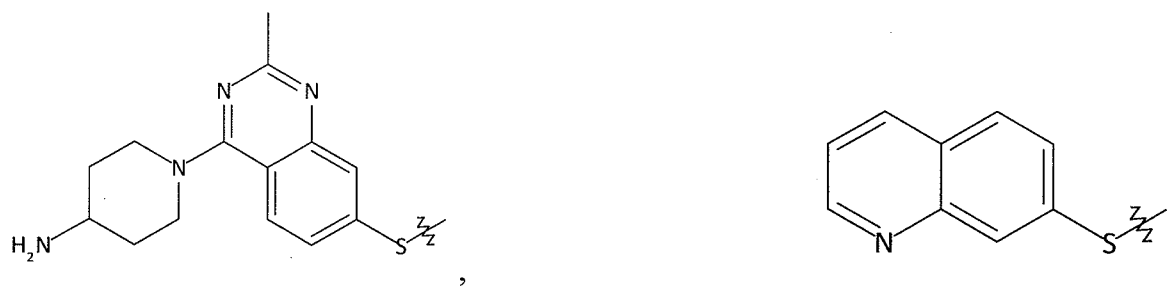
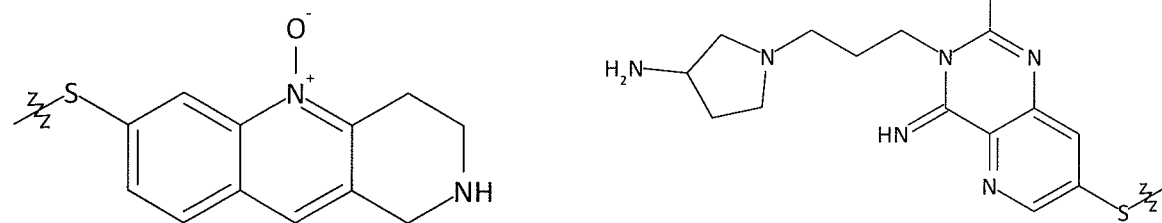
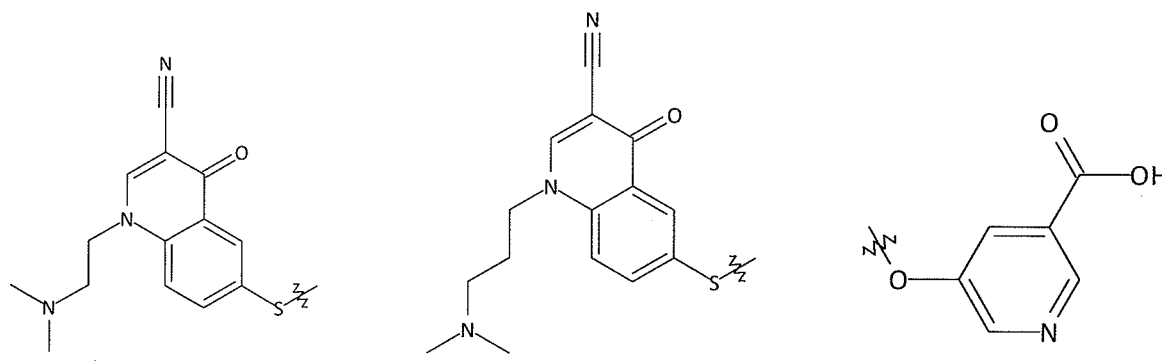
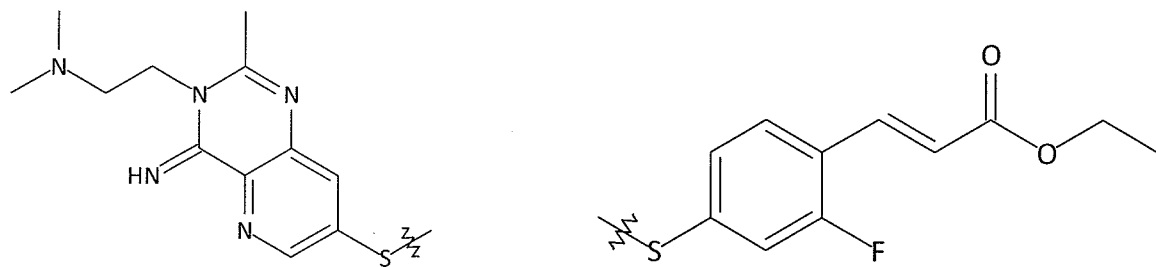


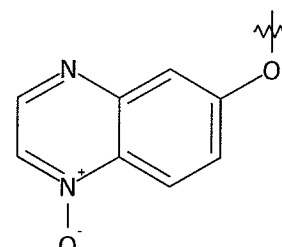
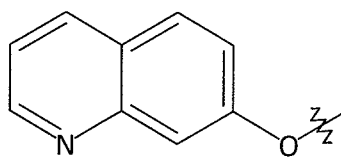
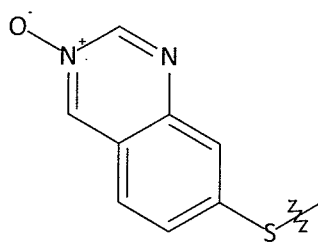
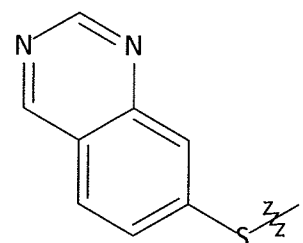
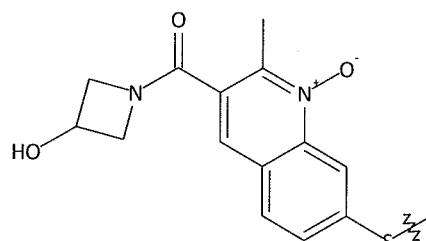
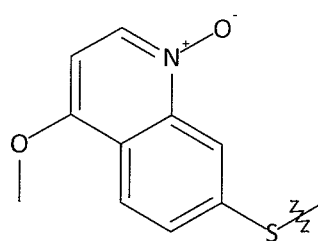
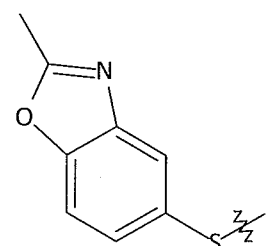
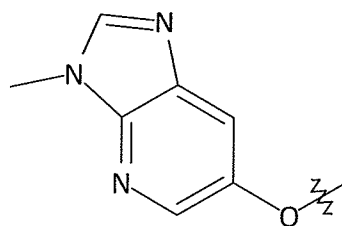
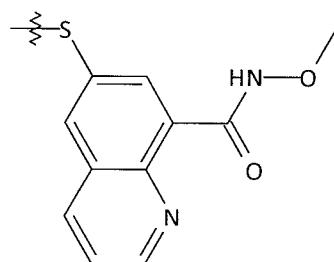
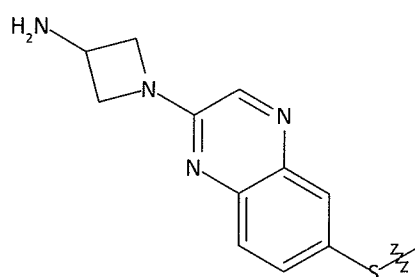
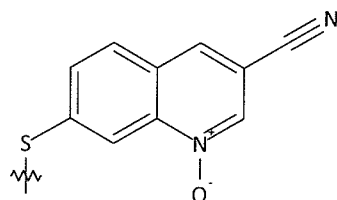
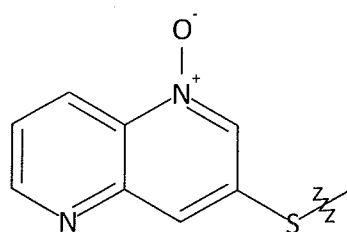
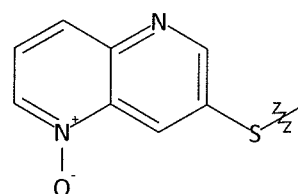
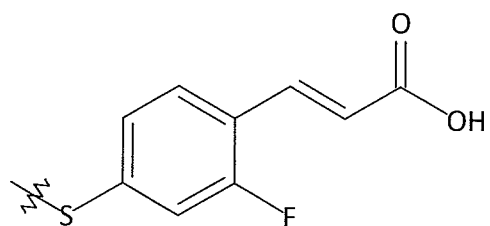
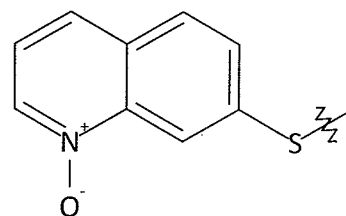
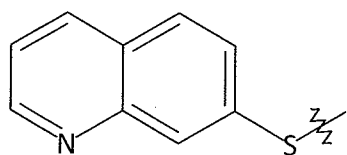


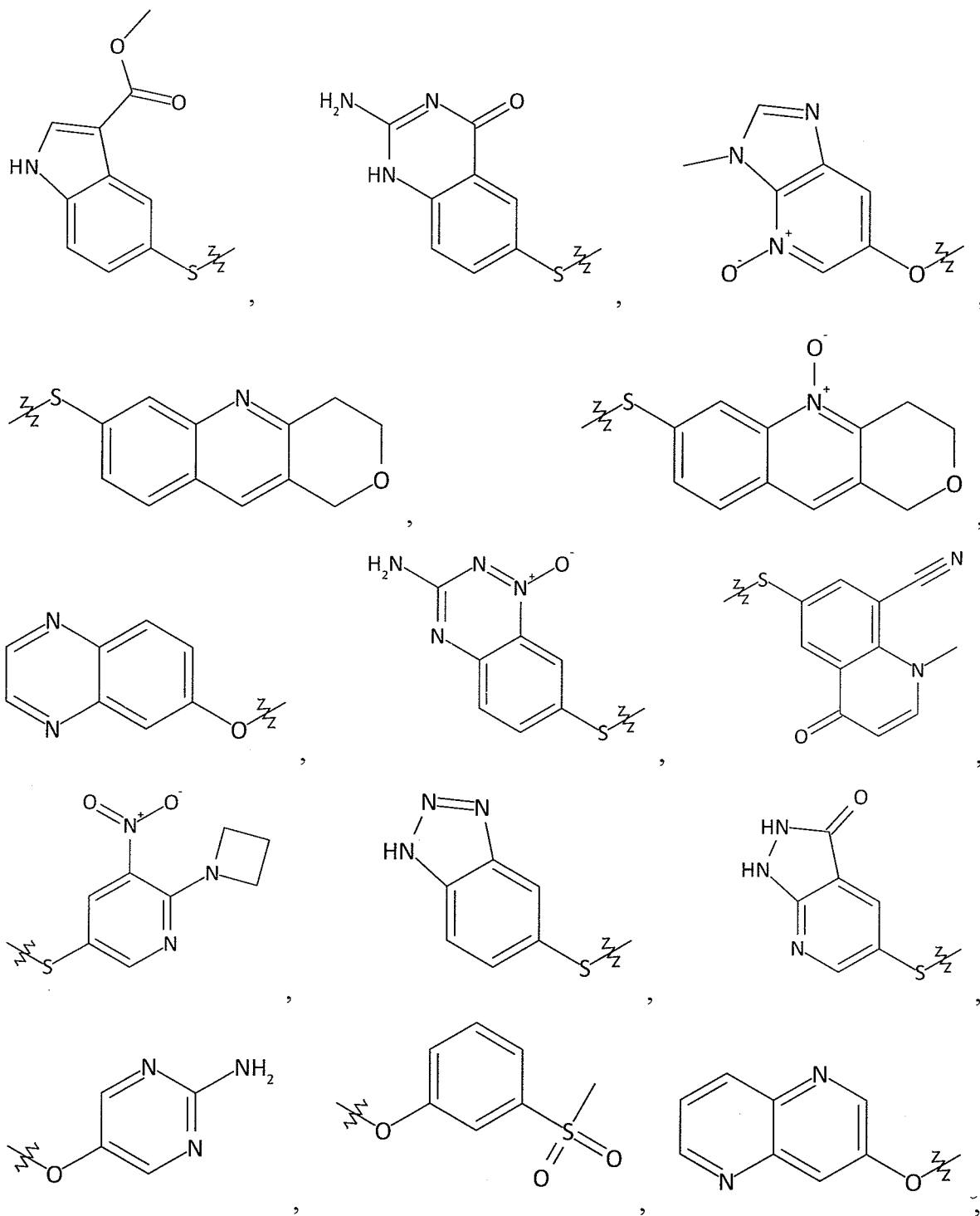


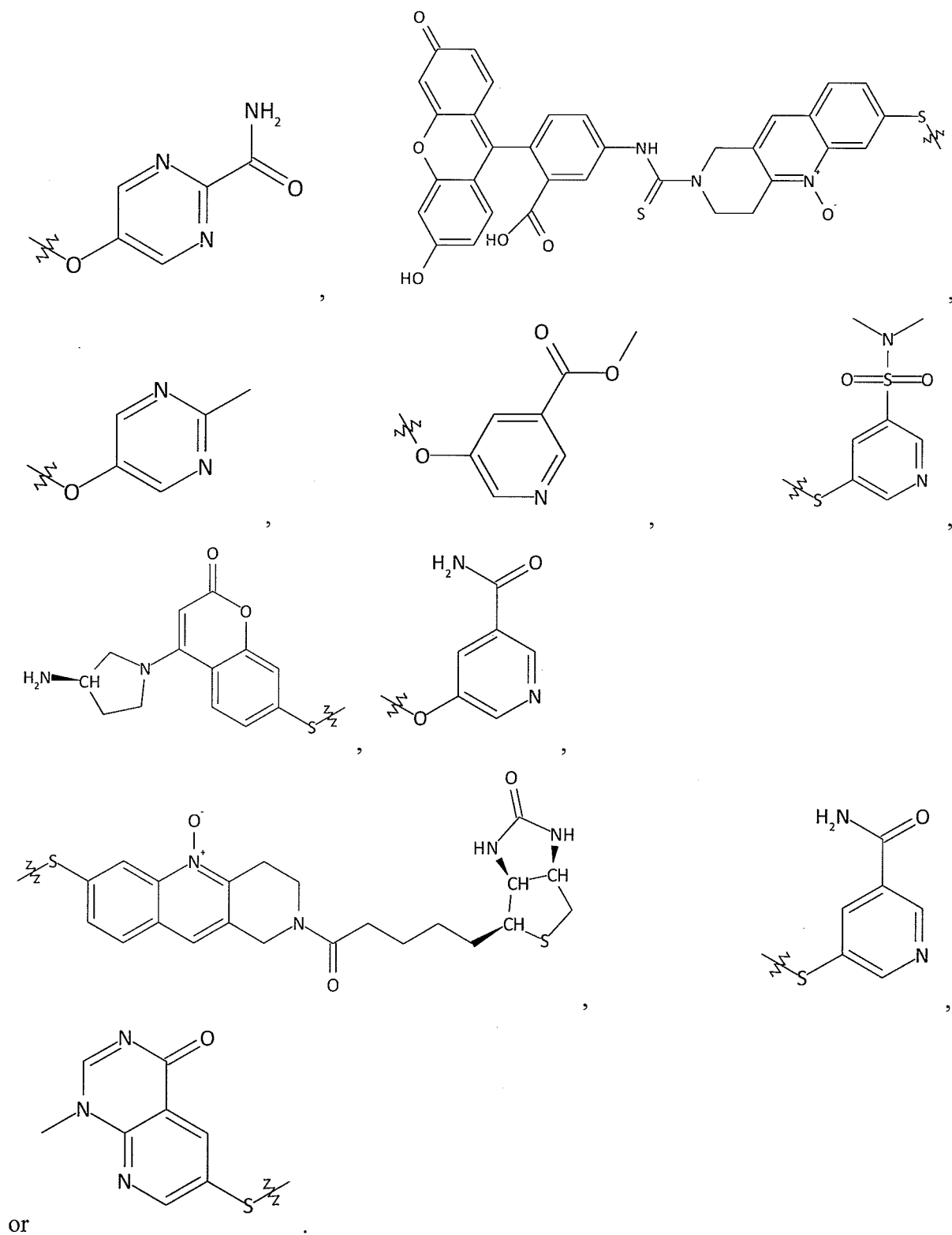












10. The compound of any of claims 1-9, wherein R^4 is

a) an inorganic residue selected from the group consisting of H, halo, OH, NH₂, SH, SO₂H, NHOH, SO₃H, SO₂NH₂, and NHSO₂NH₂;

b) an aryl C₅₋₁₄ or heteroaryl C₁₋₁₄ moiety substituted with 0-10 substituents selected from alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkylaryl, NH-aroyl, arylacyl, heteroarylacyl, halo, -O (if R⁴ contains N), OR', NR'₂, SR', SOR', SO₂R', OCOR', N-alkyl-OR', CONR'OR', NR'COR', NR'CONR'₂, NR'COOR', OCONR'₂, OR', NR'₂, COOR', alkyl-OOR', SO₃R', CONR'₂, CONR'₂OH, SO₂NR'₂, NR'SO₂NR'₂, CN, CF₃, or NO₂, wherein each R' is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-14 members;

c) alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, alkylaryl, alkenylaryl, alkynylaryl, heteroalkylaryl, heteroalkenylaryl, or heteroalkynylaryl moiety substituted with 0-10 substituents selected from the group consisting of aryl, haloaryl, arylalkyl, arylalkenyl, arylalkynyl, haloaryl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, acyl, aroyl, NH-aroyl, arylacyl, heteroarylacyl, halo, -O (if R⁴ contains N), =O, =NH, OR'', NR''₂, SR'', SOR'', SO₂R'', OCOR'', CONR''OR'', NR''COR'', NR''CONR''₂, NR''COOR'', NR''COCOOR'', OCONR''₂, COOR'', SO₃R'', CONR''₂, CONR''₂OH, SO₂NR''₂, NR''SO₂R'', NR''SO₂NR''₂, CN, CF₃, or NO₂, wherein each R'' is independently H, optionally substituted alkyl, alkenyl, alkynyl, aryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroaryl, or halo forms thereof, and wherein two of said substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-14 members; or

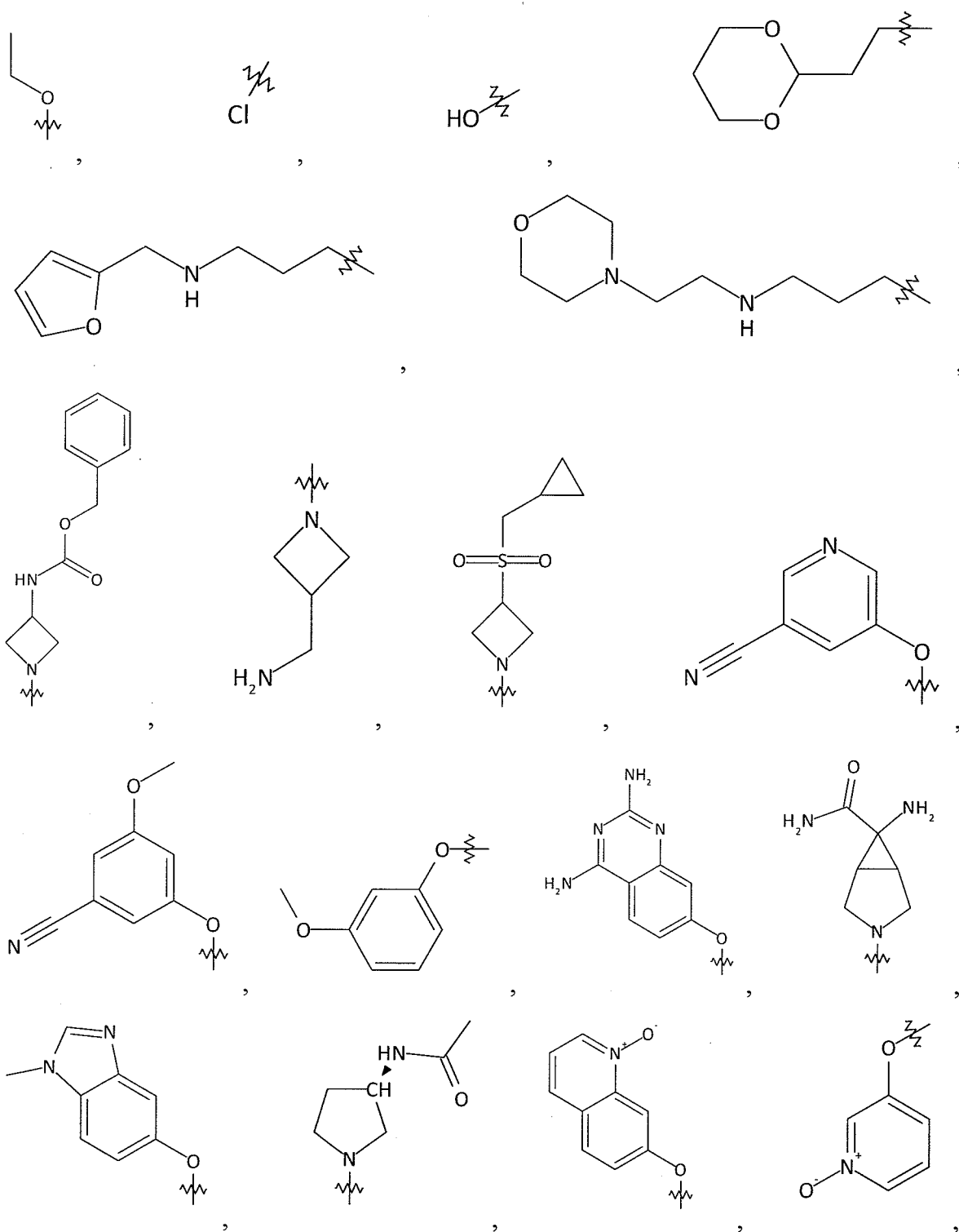
d) OR''', NR'''₂, or OSO₂R''', wherein R''' is an aryl C₅₋₁₄ or heteroaryl C₁₋₁₄, moiety substituted with 0-10 substituents selected from alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkylaryl, NH-aroyl, arylacyl, heteroarylacyl, halo, -O

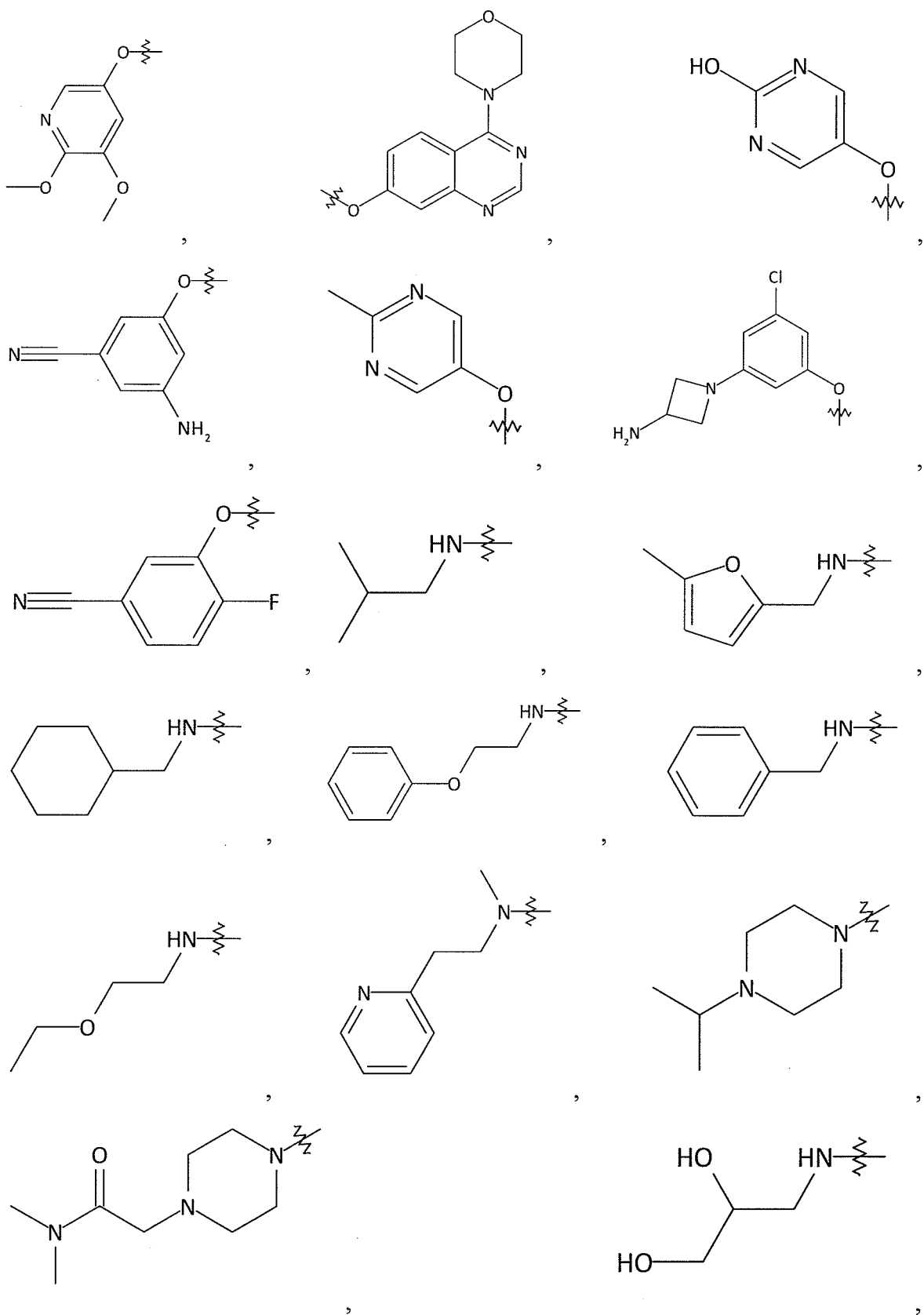
(if R^4 contains N), OR' , NR'_2 , SR' , SOR' , SO_2R' , $OCOR'$, N-alkyl- OR' , $CONR'OR'$, $NR'COR'$, $NR'CONR'_2$, $NR'COOR'$, $OCONR'_2$, $COOR'$, alkyl- OOR' , SO_3R' , $CONR'_2$, $CONR'_2OH$, $SO_2NR'_2$, $NR'SO_2NR'_2$, CN, CF_3 , or NO_2 , wherein each R' is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-14 members.

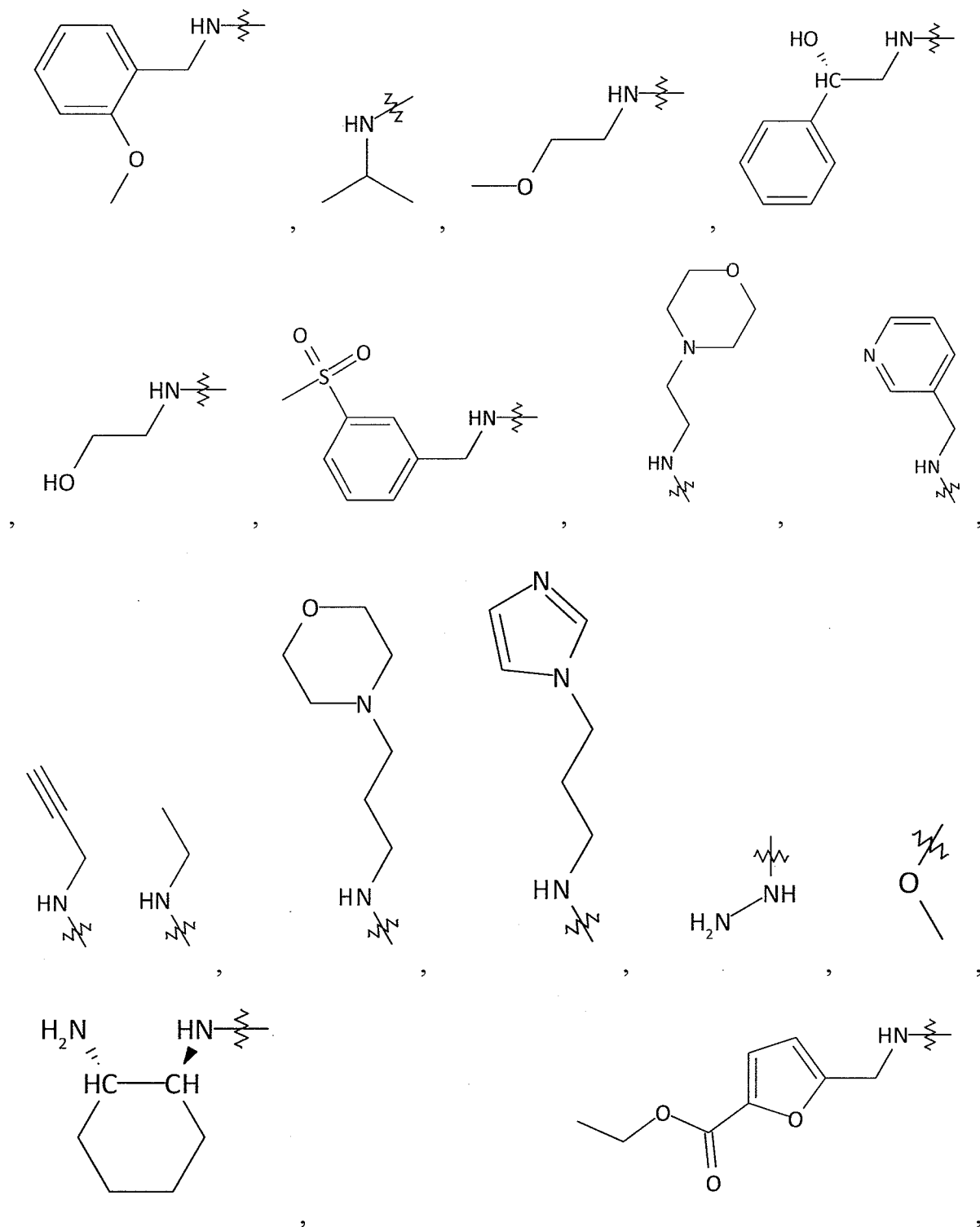
11. The compound of any of claims 1-10, wherein R^4 is selected from the group consisting of

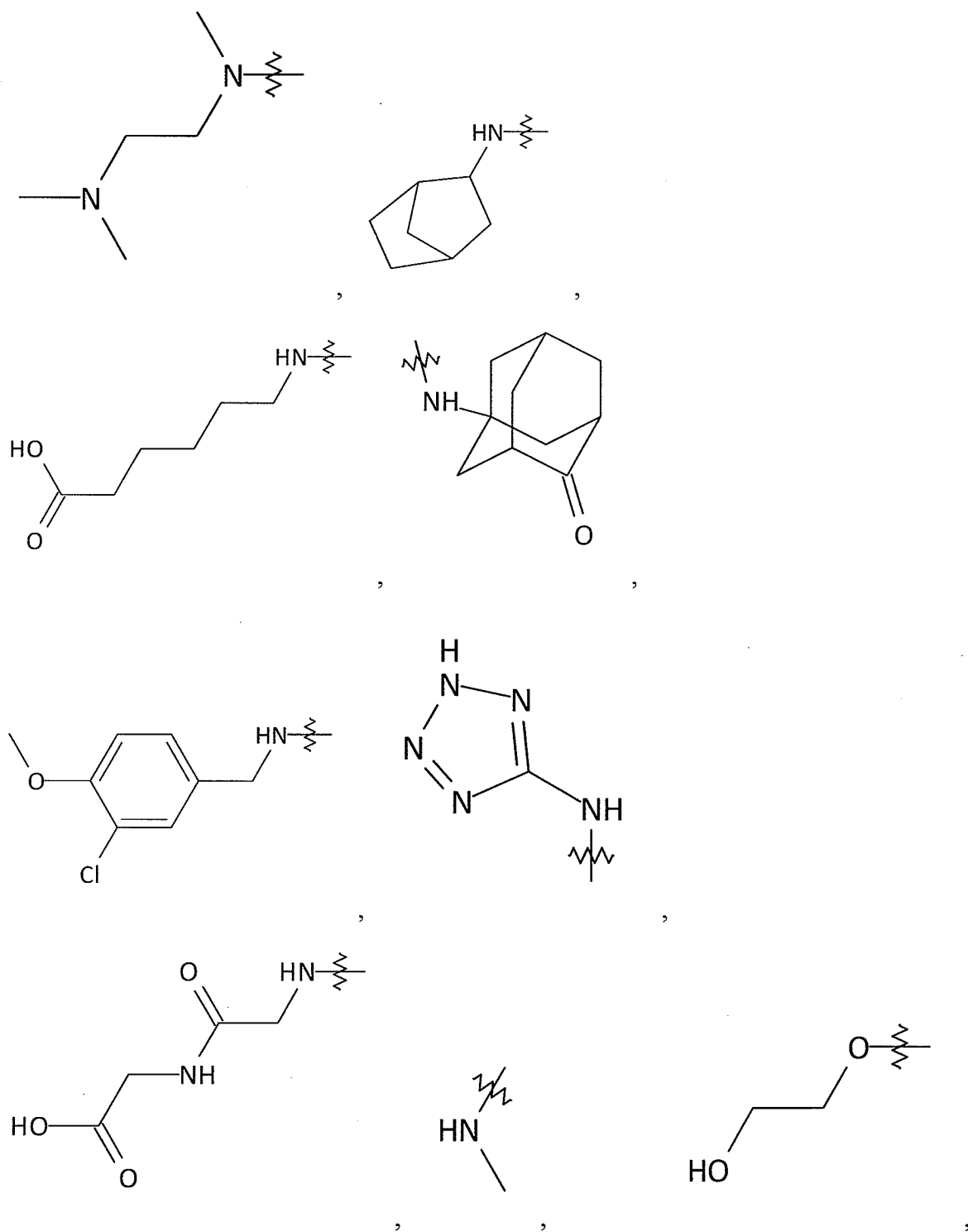
- a) H, halo, or OH;
- b) C3-6 heteroaryl moiety containing 1-4 heteroatoms selected from O, S, and N;
- c) an alkyl, alkenyl, alkenylaryl, alkylaryl, heteroalkyl, heteroalkynyl, heteroalkylaryl, moiety substituted with 0-10 substituents selected from the group consisting of: haloaryl, haloheteroaryl, heteroaryl, acyl, aroyl, NH-aroyl, halo, =O, =NH, OR'' , NR''_2 , SO_2R'' , $NR''CONR''_2$, $NR''COOR''$, $NR''COCOOR''$, $COOR''$, $NR''SO_2R''$, wherein each R'' is independently H, optionally substituted alkyl, aryl, heteroalkyl, heteroaryl, optionally substituted with one or more halo, OH, CN, or =O and wherein two of said substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-14 members; or
- d) OR''' , NR'''_2 , or OSO_2R''' , wherein R''' is aryl C_{5-14} or heteroaryl C_{1-14} , containing 1-5 O, S, or N substituted with 0-3 substituents selected from alkyl, acyl, aroyl, heteroalkyl, halo, -O (if R^4 contains N), OR' , NR'_2 , $NHCOR'$, $NHCO_2R'$, $NHCONHR'$, SO_2R' , $COOR'$, CN, wherein each R' is independently H or alkyl.

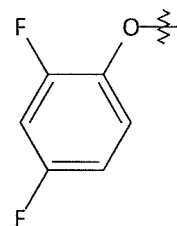
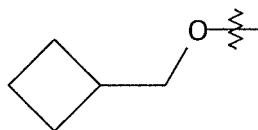
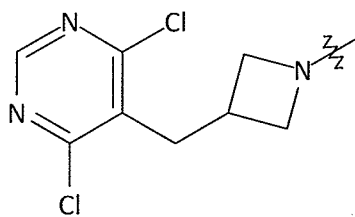
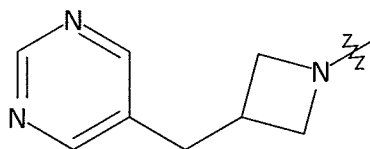
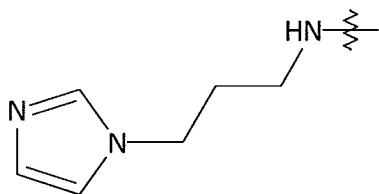
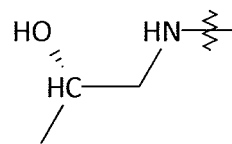
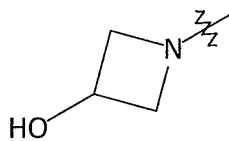
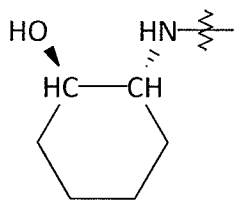
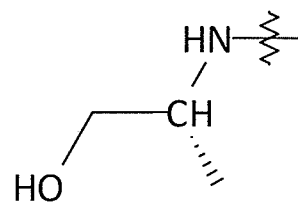
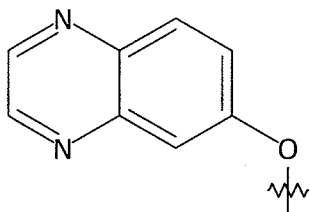
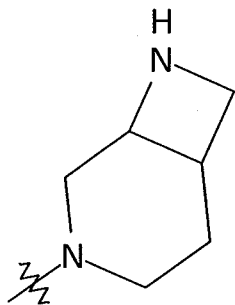
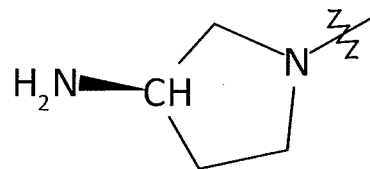
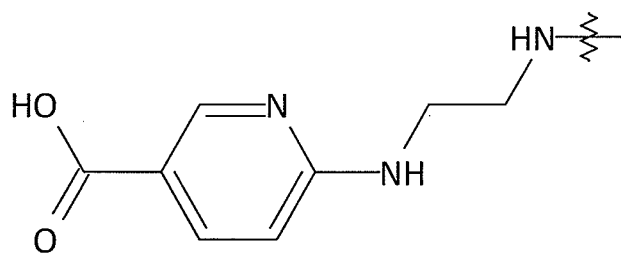
12. The compound of any of claims 1-11, wherein R^4 is selected from the group consisting of

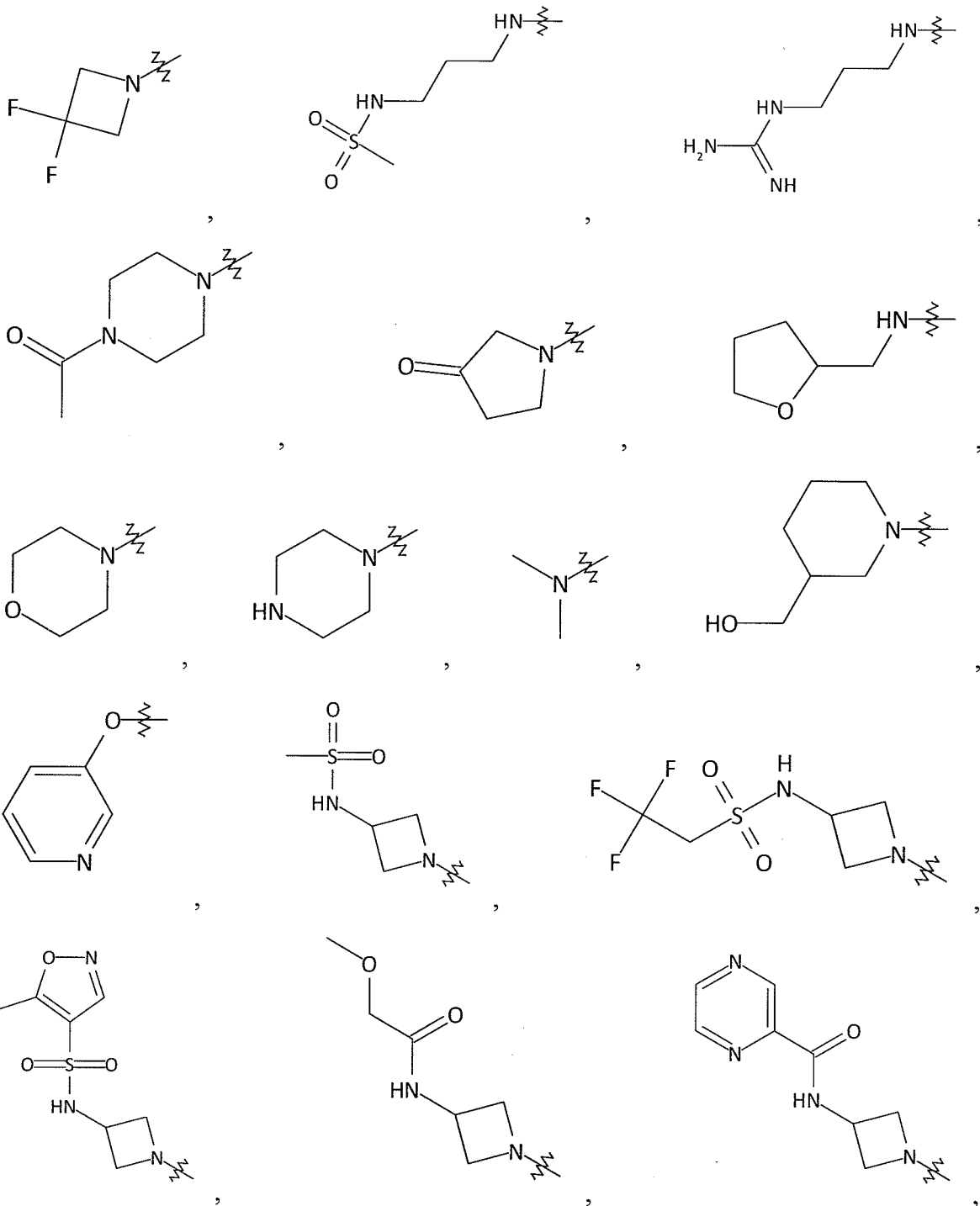


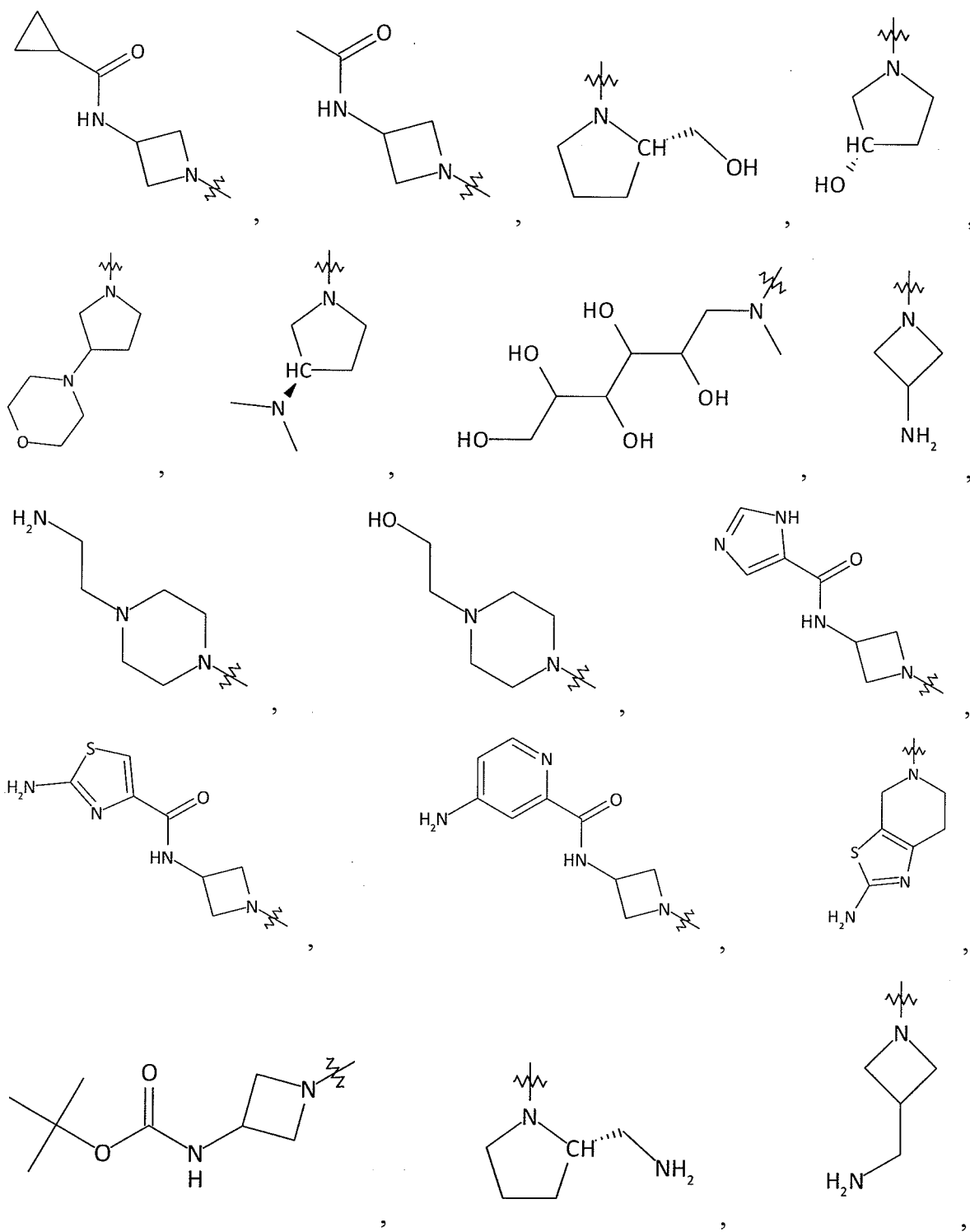


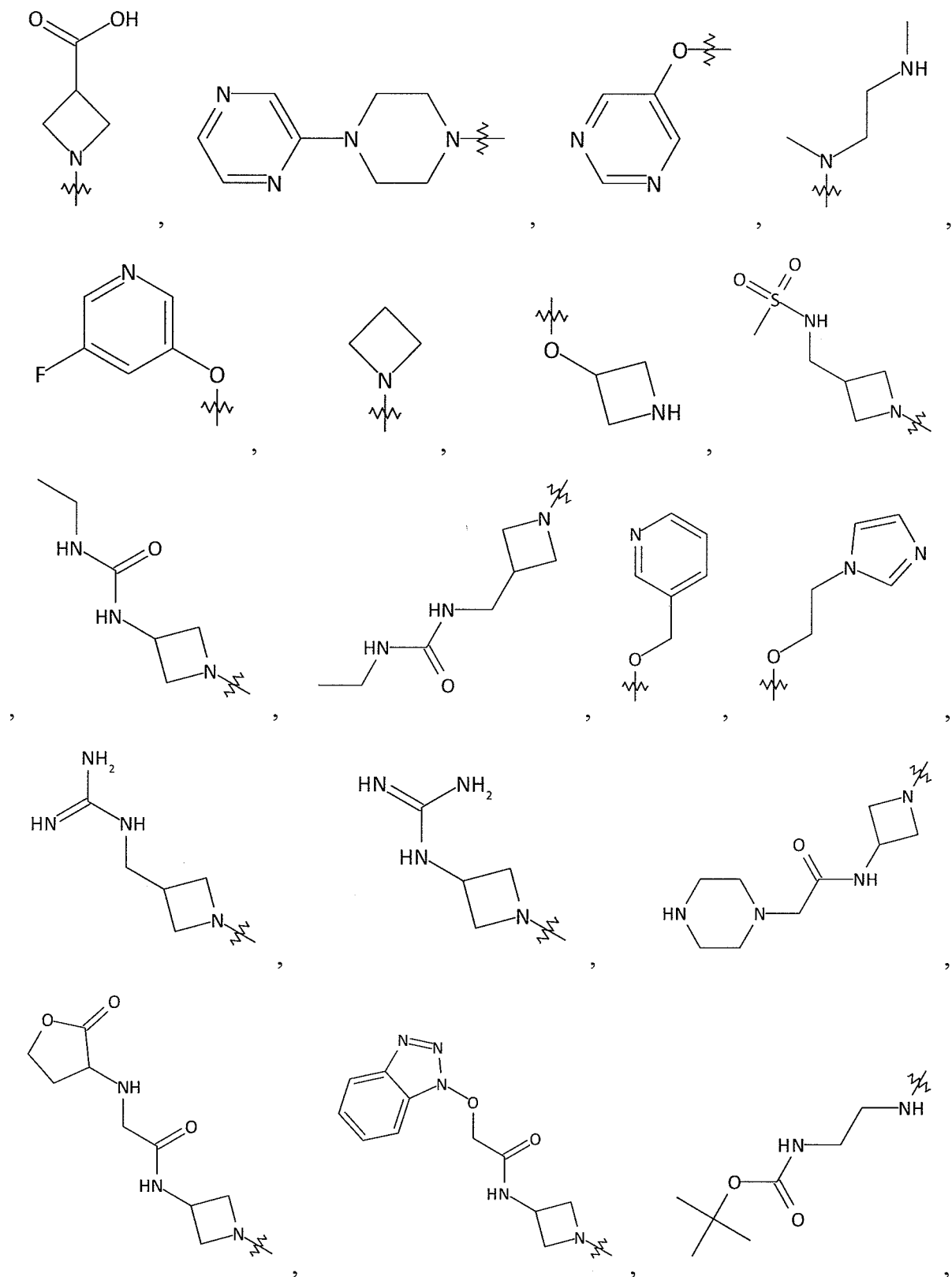


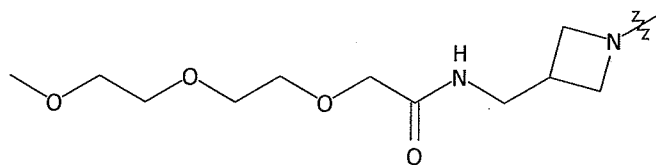
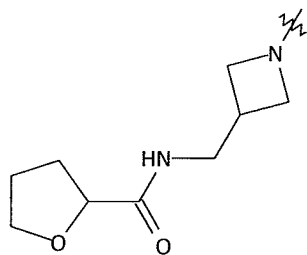
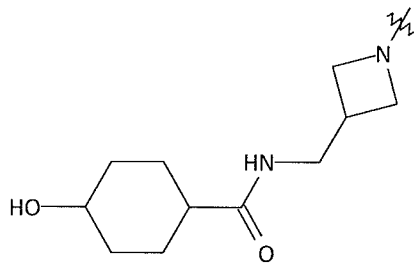
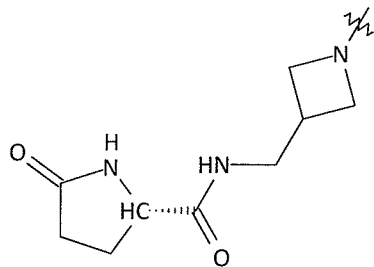
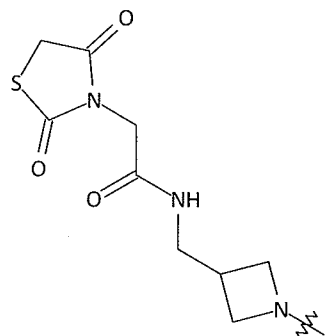
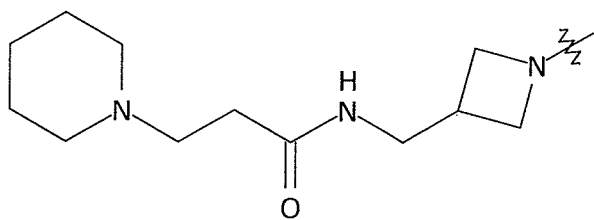
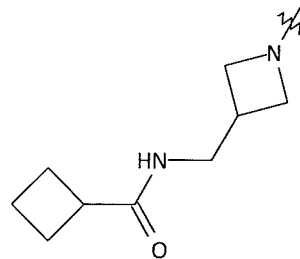
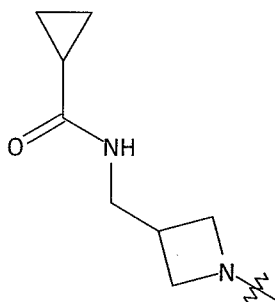
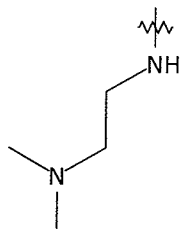
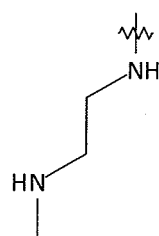
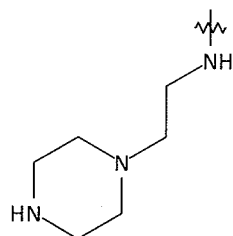
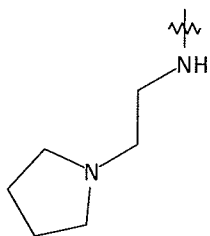
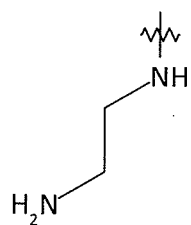


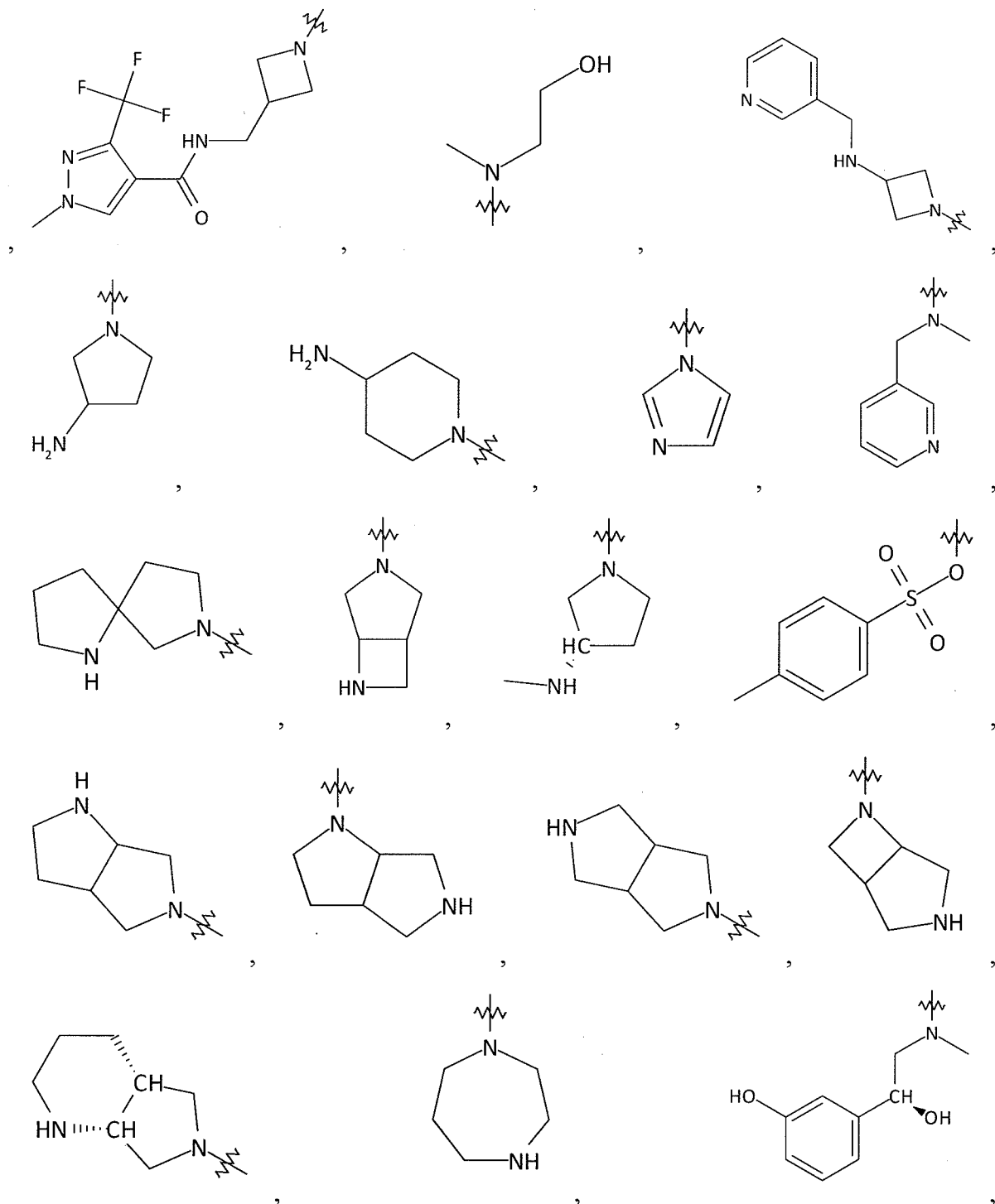


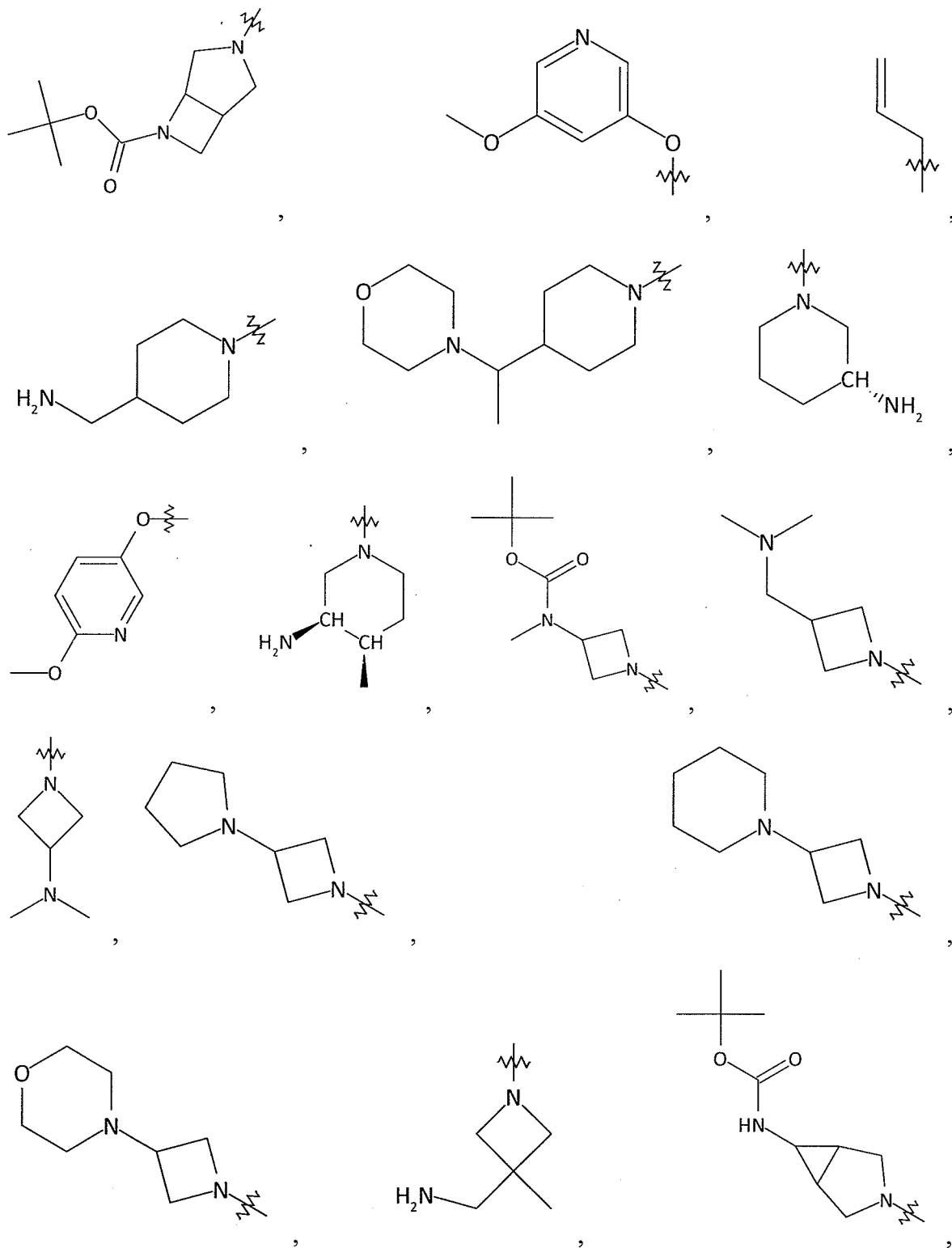


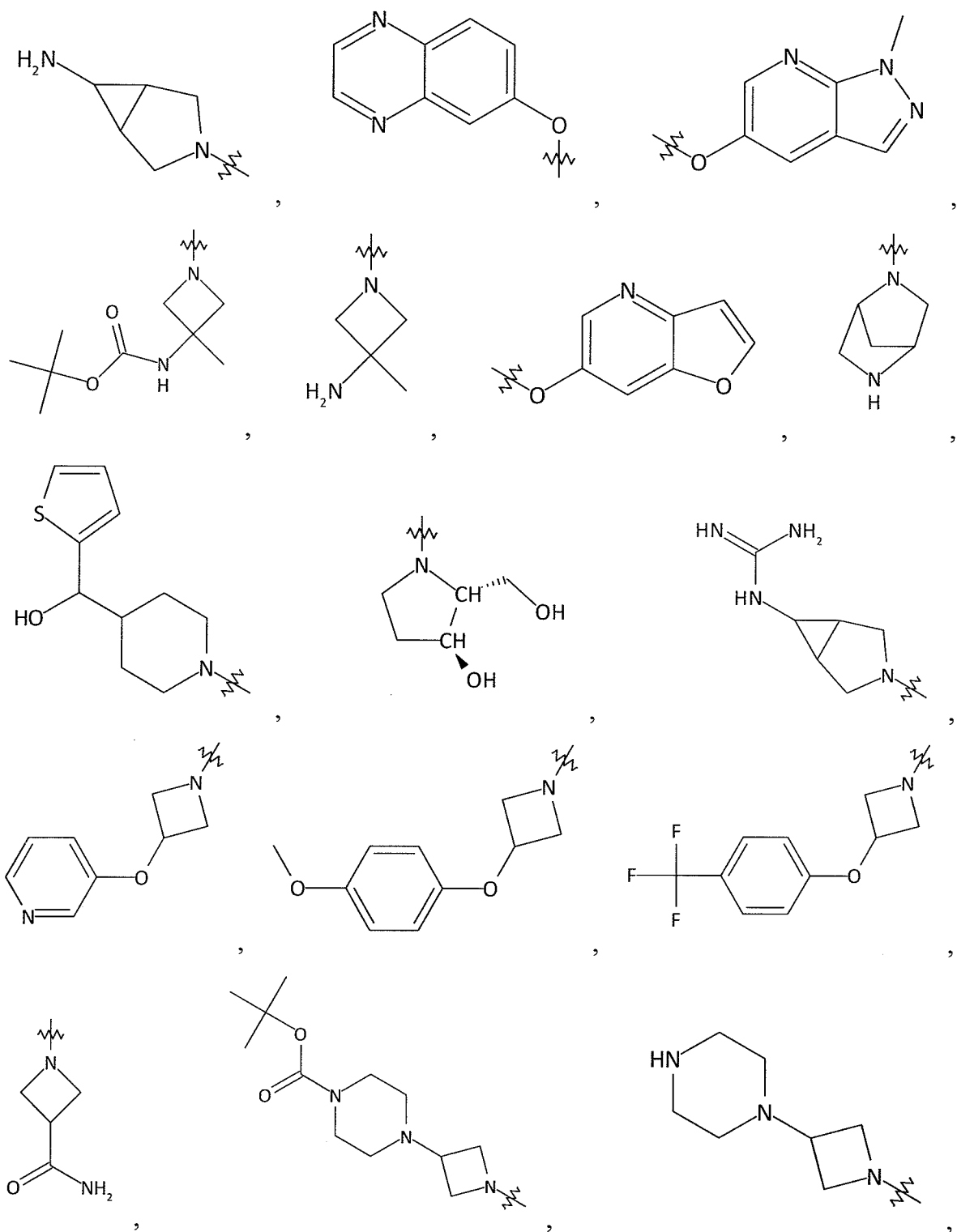


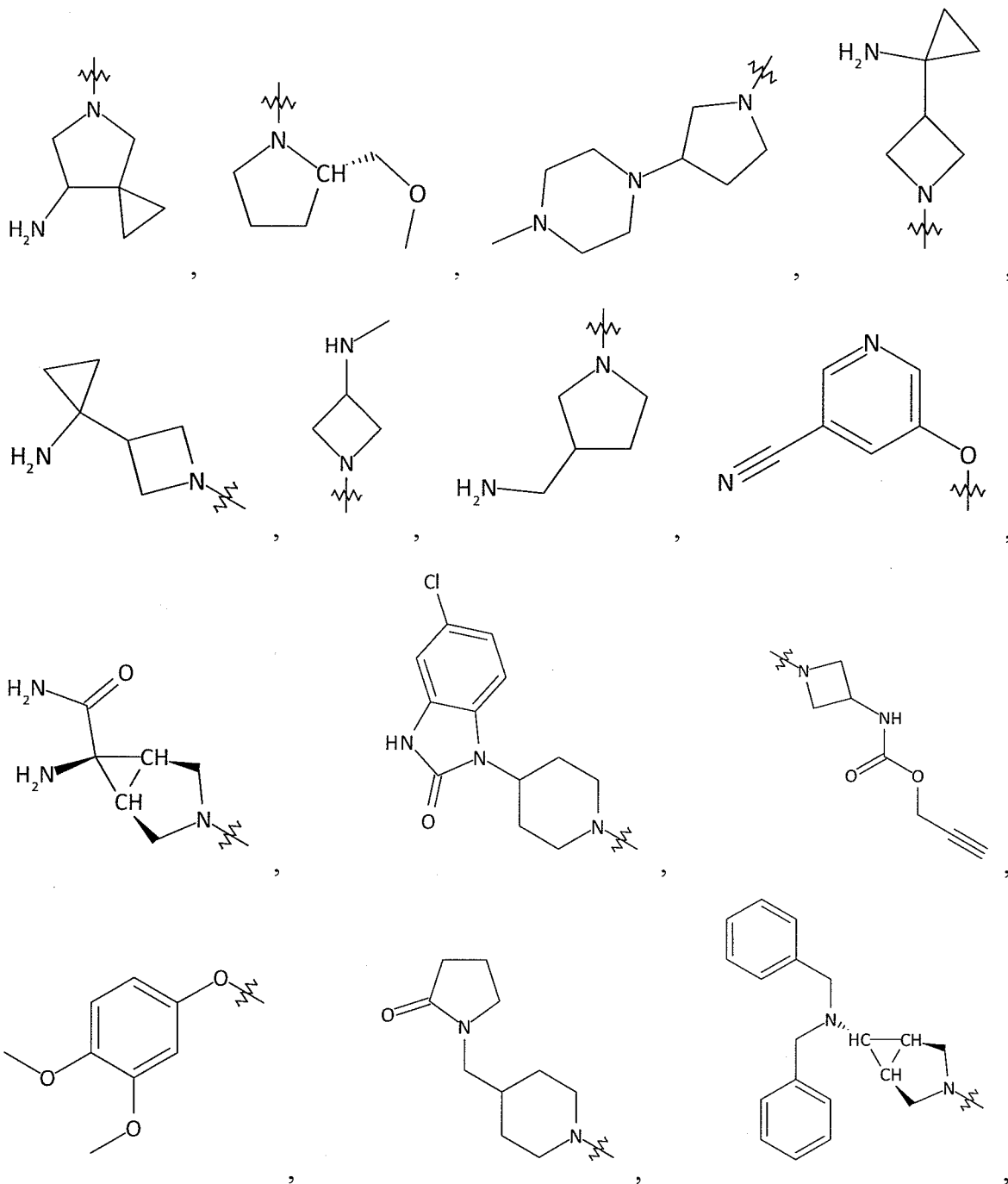


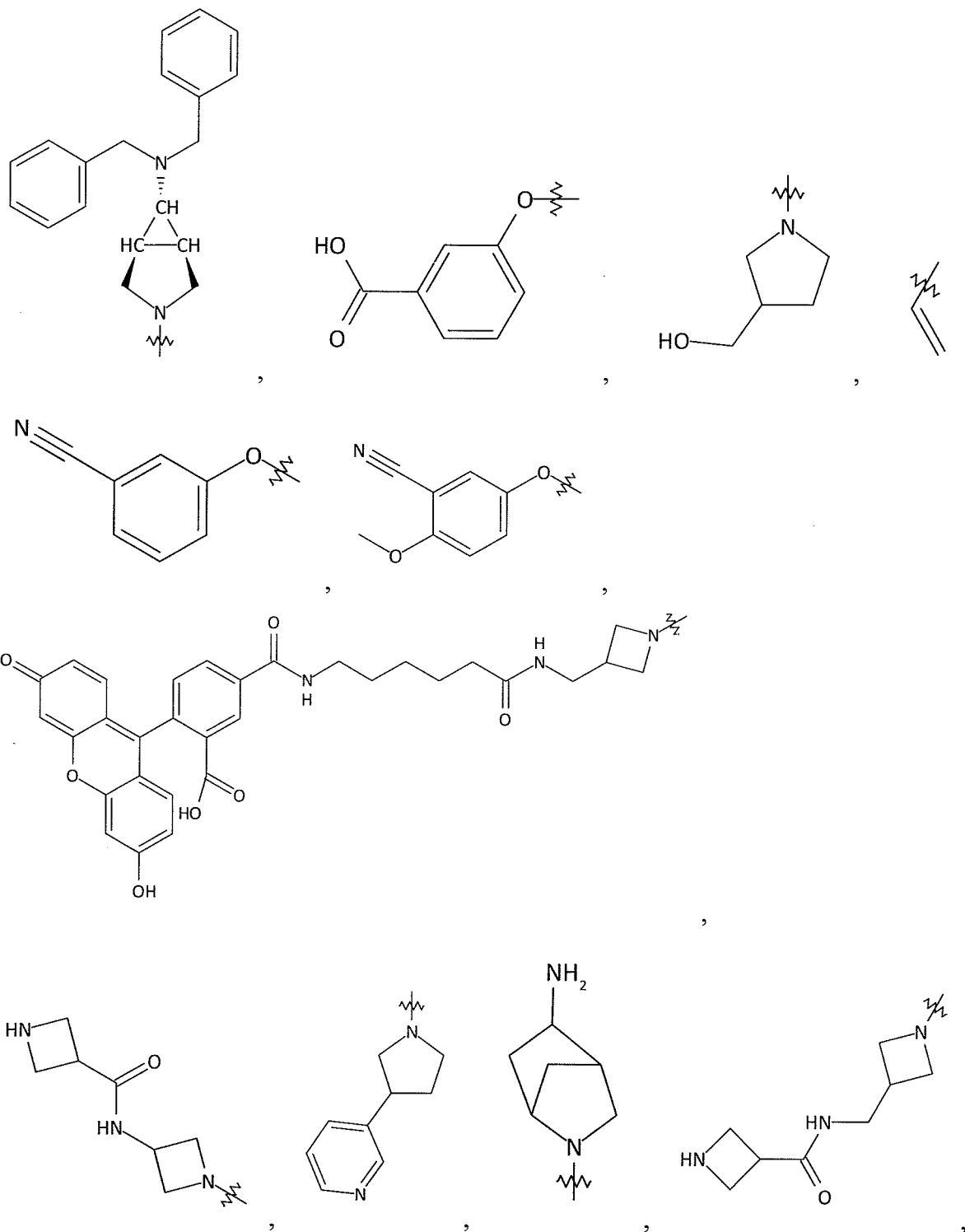


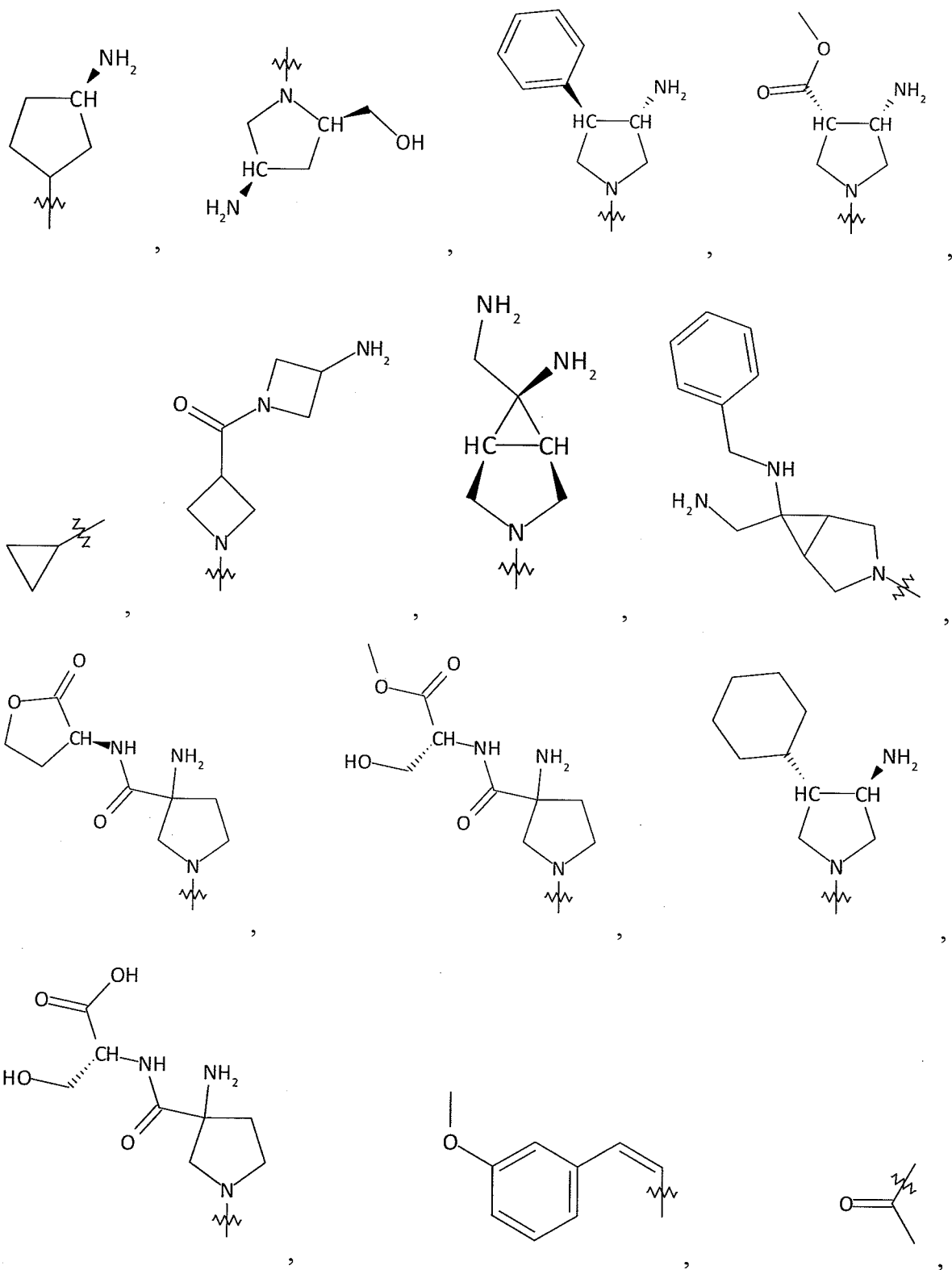


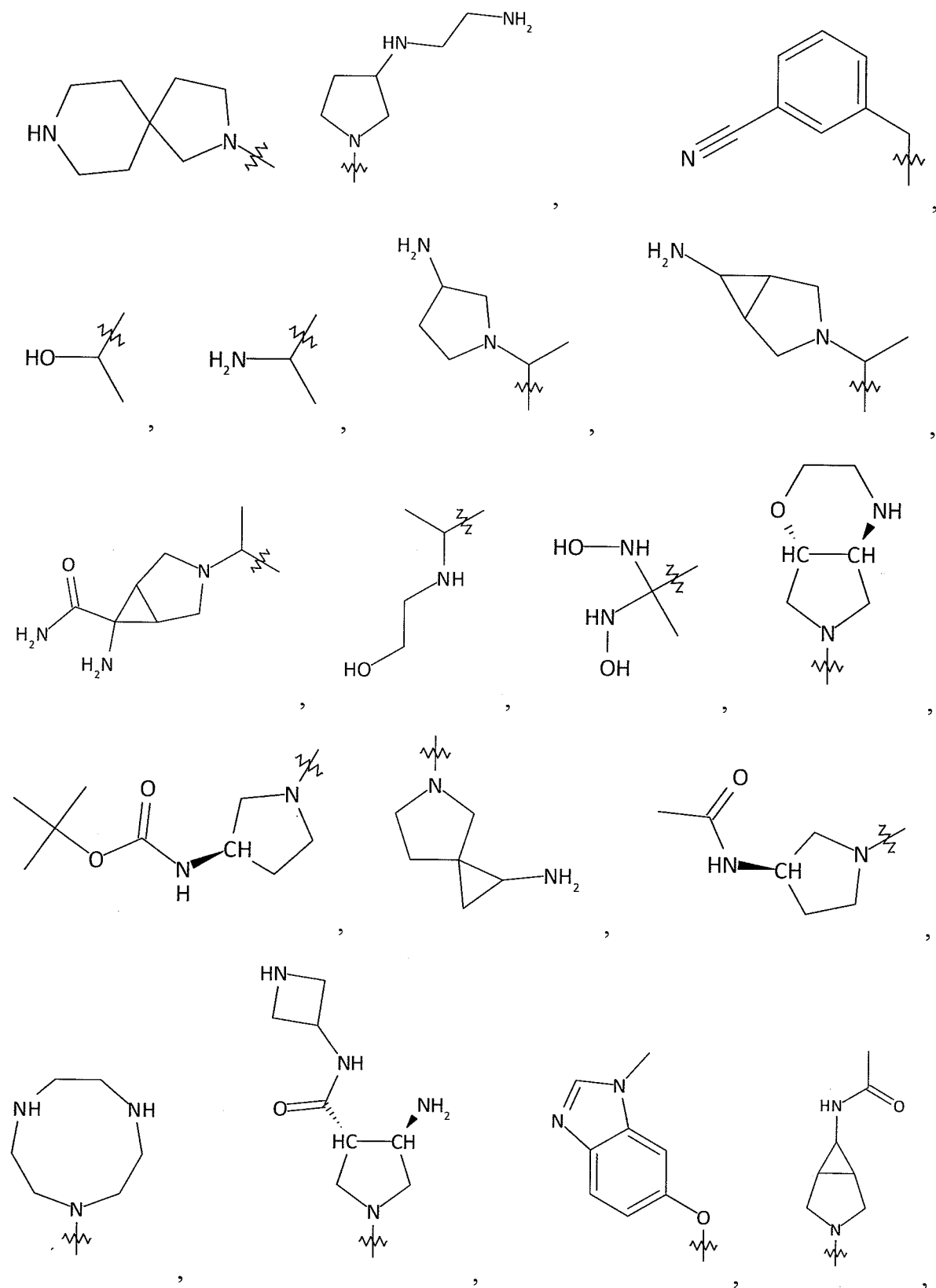


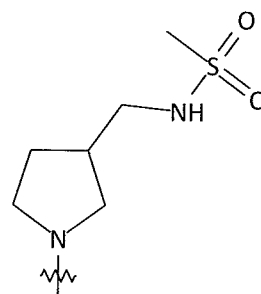
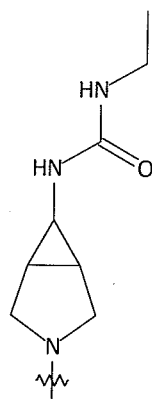
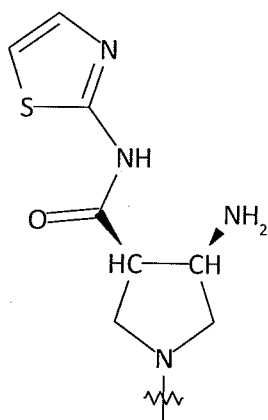
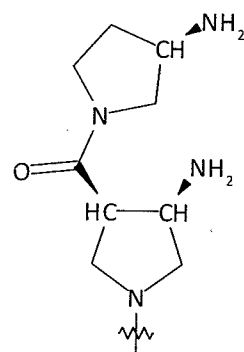
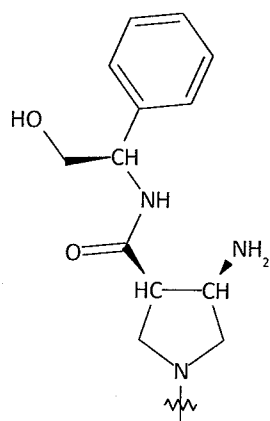
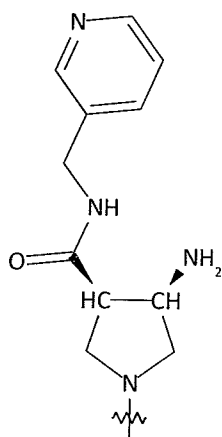
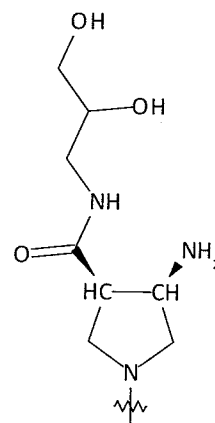
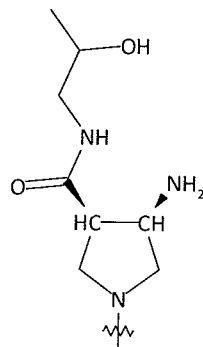
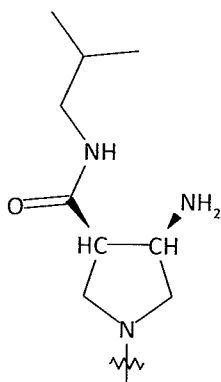
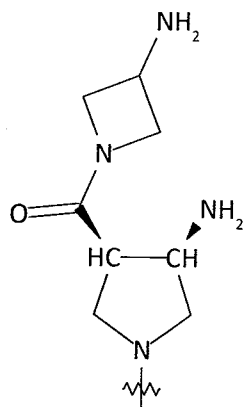


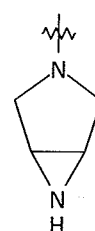
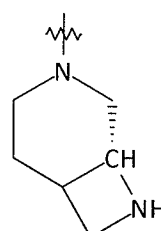
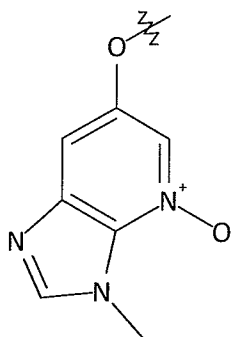
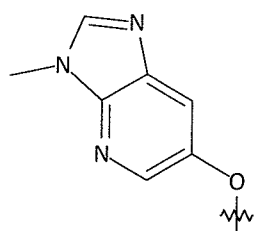
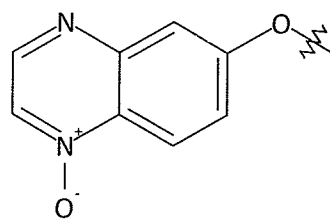
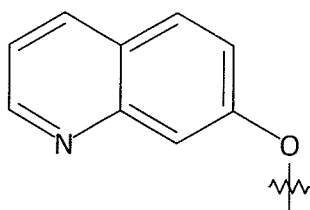
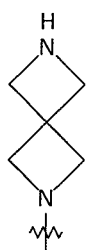
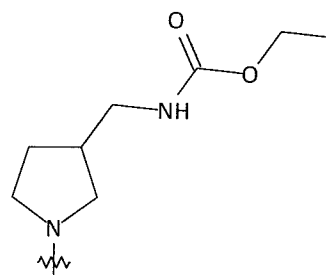
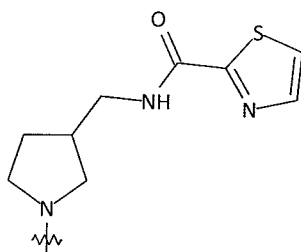
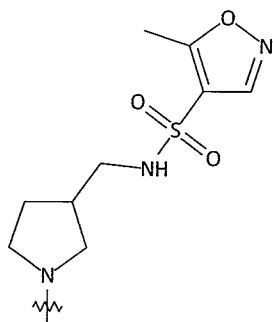
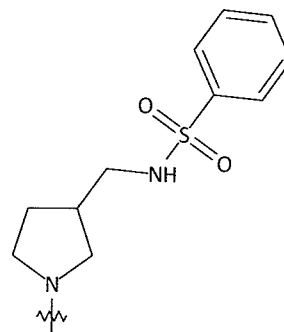
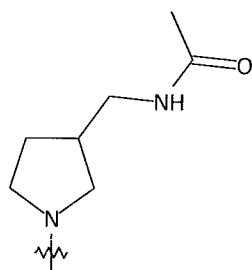
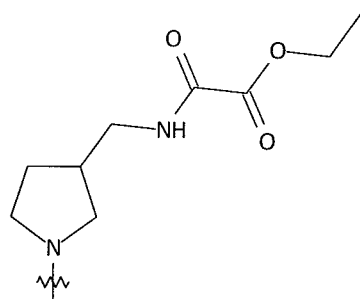


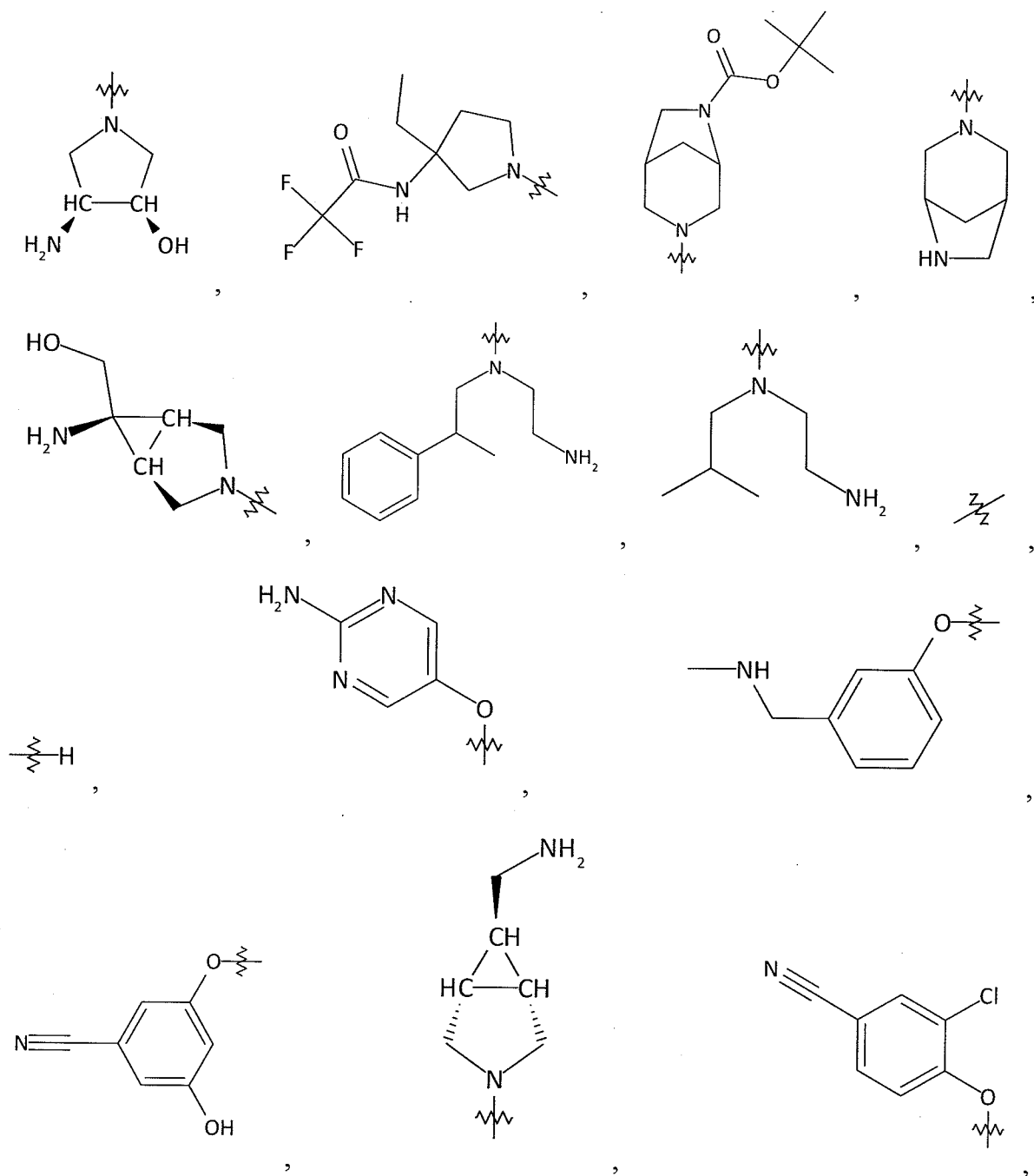


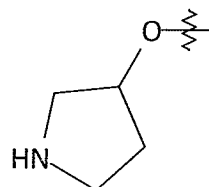
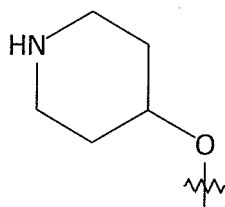
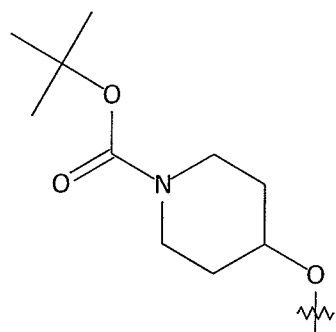




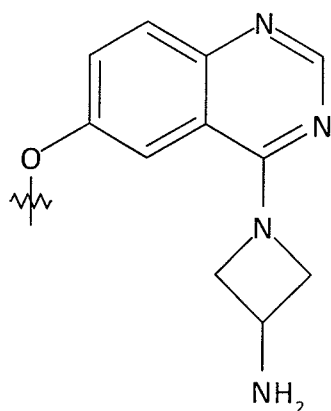




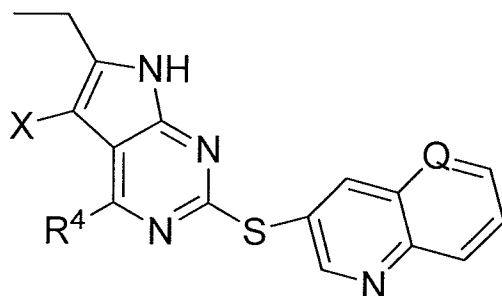




, and



13. The compound of any of claims 1-12, wherein R^6 is ethyl.
14. The compound of any of claims 1-13, having the structure of Formula II



wherein X is halogen;

R^4 is an amine-substituted heteroalicyclic ring; and

Q is N or N^+-O^- .

15. The compound of any of claims 1-14,
wherein X is Cl or Br;

wherein R^4 is a 4-7 membered heteroalicyclic ring containing an N heteroatom; and

wherein the 4-7 membered heteroalicyclic ring is substituted with NH_2 .

16. The compound of any of claims 1-14,

wherein X is Cl;

wherein R^4 is a 5-6 membered heteroalicyclic ring having one N heteroatom in the backbone of the ring;

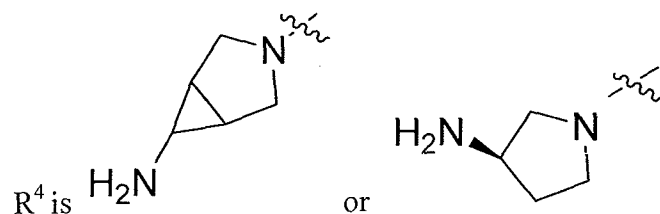
wherein the N heteroatom is directly linked to the remainder of the compound;

and

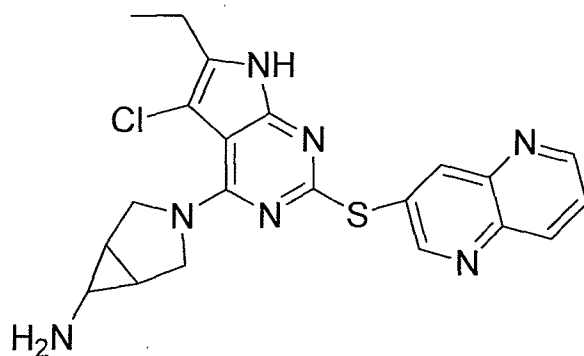
wherein the 5-6 membered heteroalicyclic ring is substituted with one NH_2

substituent.

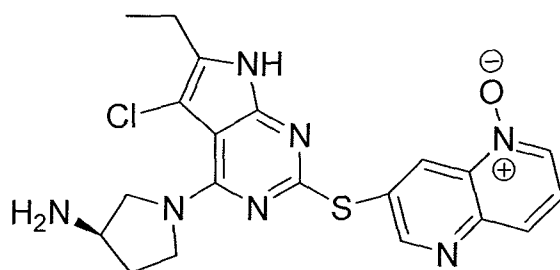
17. The compound of claim any of claims 1-14,



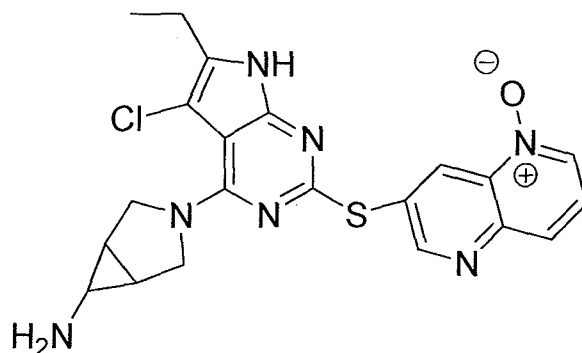
18. The compound of any of claims 1-17 which is



19. The compound of any of claims 1-17 which is



20. The compound of any of claims 1-18 which is



21. The compound of claim 1 selected from the group consisting of the compounds in Table 1.
22. A pharmaceutical composition comprising the compound of any of claims 1-21.
23. A method of making a compound of any of claims 1-21 comprising deprotecting a protected form of a compound of Formula I wherein Z is C-halo.
24. The method of making a compound of claim 23 comprising before the deprotecting step
halogenating a protected form of the compound of Formula I wherein Z is CH to form a compound of Formula I wherein Z is C-halo.
25. A method of making a compound of any of claims 1-21 comprising
halogenating a compound of Formula I wherein Z is CH to form a compound of Formula I wherein Z is C-halo.
26. A method of inhibiting the growth of bacteria, comprising exposing the bacteria to a compound or composition of any of claims 1-22.

27. A method of treating a mammal suffering from a bacterial infection, comprising administering to the mammal an effective dose of a compound or composition of any of claims 1-22.