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(54) Title: EMS ANALOGUES OF LYN/SRC-TYROSINE KINASE INHIBITORS

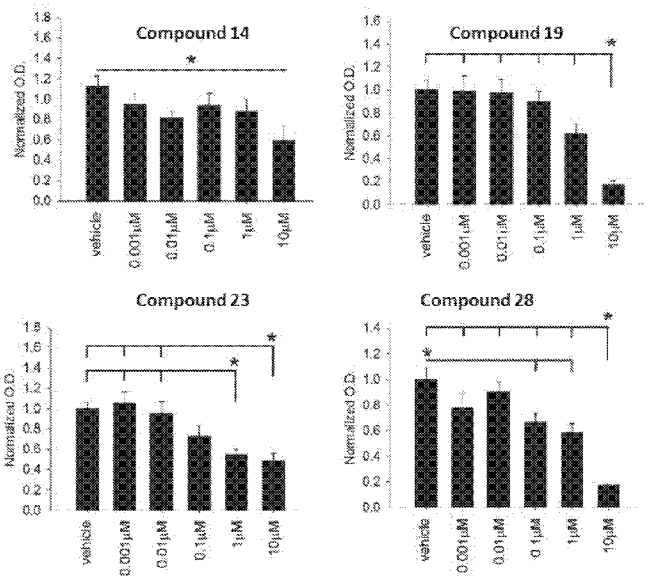


FIG. 1

(57) Abstract: Embodiments of the present invention are directed to compounds of the formula API—LG—ESM wherein "API" is a monovalent substituent group of an enzyme inhibitor; "LG" is a divalent substituent group of a linking group; and "ESM" is a monovalent substituent group of an esterase sensitive motif; or a pharmaceutically acceptable salt thereof. Other embodiments are directed to methods for using compounds of the formula API—LG—ESM to treat a number of medical conditions, including Alzheimer's disease.

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EMS ANALOGUES OF LYN/SRC-TYROSINE KINASE INHIBITORS

PRIORITY

[0001] This Application claims the benefit of U.S. Provisional Application Serial No. 62/265,673, filed December 10, 2015.

STATEMENT OF GOVERNMENT SUPPORT

[0002] This invention was made with government support under grant 5P30GM103329 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

[0003] Generating selective drugs that specifically affect (e.g., inhibit) protein kinase function and that are useful in treating a whole host of diseases remains a challenge and new strategies are required. Disease conditions often demonstrate increased kinase activity in particular cells as a causative or exacerbating condition of disease. Therefore, the ability to inhibit the kinases in only the specific cells of interest is a clear therapeutic goal. However, kinases are typically expressed in many cells in a tissue or organ making classic small molecule kinase inhibitor strategies less than ideal since the drugs cannot discriminate between cell types. This lack of specificity in classic drug design results in unwanted or adverse effects of many kinase inhibitor approaches. For example, the Src family of kinases are activated in immune cells such as macrophages and microglia during a variety of disease or degenerative conditions. Activation of this family of kinases is key to the ability of these cells to contribute to the disease or degenerative process. However, as already mentioned, chronic inhibition of this widely expressed family of kinases would have adverse effect in many organs due to the wide expression pattern and functions that they serve.

SUMMARY

[0004] This disclosure describes the design and testing of a small molecule strategy that allows for inhibition of kinases, such as Src family kinases, in a fashion that is selective for high esterase activity containing cells such as macrophages and microglia. The approach described herein allows an esterase cleavable pro-drug to be administered at very low (e.g., from about 1 nM to about 10 μM; about 10 nM to about 100 nM; about 100 nM to about 1 μM; or about 10 μM) concentrations resulting in uptake by all cells, but intracellular accumulation of the esterase cleaved active drug in only cells such as

macrophages and microglia. The outcome of this strategy is the ability to provide low concentration of prodrug insufficient to inhibit kinases and demonstrate anti-inflammatory effects in other cells, but robust kinase inhibitory, anti-inflammatory effects in macrophages and microglia to effectively provide a cell-selective small molecule kinase inhibitors. This strategy can be extended to numerous families of kinases or other enzymatic activities in microglia and monocytic lineage cells.

[0005] Compounds of the various embodiments described herein have demonstrated protein kinase inhibitory activity in a dose-dependent fashion. In addition, compounds of the various embodiments described herein show selectivity for certain protein tyrosine kinases, including Src.

[0006] The present invention provides for the compounds of formula (I), (IV), and (V), as illustrated herein. The present invention also provides for a pharmaceutical composition that includes one or more of the compounds of formula (I), (IV), and (V), in combination with a pharmaceutically acceptable carrier.

[0007] The present invention provides for one or more of the compounds of formula (I), (IV), and (V), for use in medical treatment or therapy of an animal. The animal can include humans. Additionally, the medical treatment or therapy can include, e.g., at least one of: targeting cells of monocytic origin; targeting microglia; inhibiting at least one of: Lyn, Src, IKK, ERK, JNK, p38, calcineurin, and LRRK2; selectively accumulating in microglia; penetrating the blood-brain barrier; treating inflammation of the peripheral nervous or organ systems; treating rheumatoid arthritis; treating irritable bowel syndrome (IBS); treating inflammation in the central nervous system (CNS); treating inflammation in the peripheral nervous system (PNS); treating Alzheimer's disease (AD); treating Parkinson's disease (PD); treating cancer; treating Crohn's disease; treating respiratory distress syndrome; treating glomerulonephritis; and treating pulmonary emphysema.

[0008] The present invention provides for one or more of the compounds of formula (I), (IV), and (V), for use in medical treatment or therapy of an animal. The animal can include humans. Additionally, the medical treatment or therapy can include, e.g., at least one of: targeting cells of monocytic origin; targeting microglia; inhibiting at least one of: Lyn, Src, IKK, ERK, JNK, p38, calcineurin, and LRRK2; selectively accumulating in microglia; penetrating the blood-brain barrier; treating inflammation of the peripheral nervous or organ systems; treating rheumatoid arthritis; treating irritable bowel

syndrome (IBS); treating inflammation in the central nervous system (CNS); treating inflammation in the peripheral nervous system (PNS); treating Alzheimer's disease (AD); treating Parkinson's disease (PD); treating cancer; treating Crohn's disease; treating respiratory distress syndrome; treating glomerulonephritis; and treating pulmonary emphysema.

DESCRIPTION OF THE DRAWINGS

[0009] FIG. 1 is plots of normalized optical density (OD) of western blotted anti-pSrc in primary murine microglia as a function of compound concentration, for compounds 14, 19, 23, and 28.

[0010] FIG. 2 is plots of normalized optical density (OD) of western blotted pERK in primary murine microglia as a function of compound concentration, for compounds 14, 19, 23, and 28.

[0011] FIG. 3 is plots of pg/mL TNFα secreted from primary murine microglia (panel (a)) and primary murine astrocytes (panel (b)) compound 19.

[0012] FIG. 4 is plots of pg/mL TNFα secreted from primary murine microglia (panel (a)) and primary murine astrocytes (panel (b)) compound 23.

DESCRIPTION

[0013] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in part in the accompanying drawings. While the invention will be described in conjunction with the enumerated claims, it will be understood that the exemplified subject matter is not intended to limit the claims to the invention.

[0014] The present disclosure provides compounds of formula (I), as illustrated herein:

API—LG—ESM

(I)

wherein "API" is a monovalent substituent group of an enzyme inhibitor; "LG" is a divalent substituent group of a linking group; and "ESM" is a monovalent substituent group of an esterase sensitive motif; or a pharmaceutically acceptable salt thereof.

[0015] The present disclosure also provides compounds of the formulae (IV) and (V):

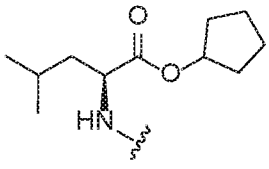
[Dasatinib] – [LG] – [cyclo-pentyl ester of L-leucine]

(IV)

[Bafetinib] – [LG] – [cyclo-pentyl ester of L-leucine]

(V)

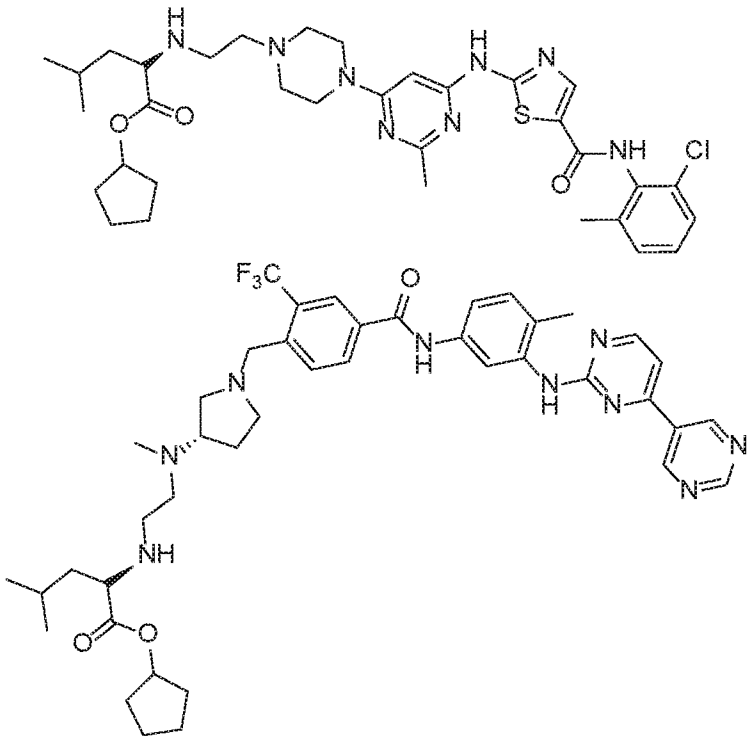
wherein the esterase sensitive motif (ESM), "cyclopentyl ester of L-leucine," has the formula:



; and

LG is a divalent substituent group of a hydrocarbon comprising at least one of alkyl, alkenyl, nitrogen-containing heterocyle, and nitrogen-containing heteroaryl; wherein each of the alkyl, alkenyl, nitrogen-containing heterocyle, and nitrogen-containing heteroaryl is independently optionally substituted and is optionally interrupted.

[0016] Specific compounds falling under the formulae (IV) and (V) are compounds of the formulae:



, respectively.

[0017] In some embodiments, the API is a monovalent substituent group of an enzyme inhibitor whose action results in inhibition of cytokine gene expression, production, secretion or activity.

[0018] In some examples, the API is a monovalent substituent group of a protein kinase inhibitor. In other examples, the API is a monovalent substituent group of a protein tyrosine kinase inhibitor. In still other examples, the API is monovalent substituent group of at least one of an ABL-family protein

kinase inhibitor, focal adhesion kinase (FAK)-family protein kinase inhibitor, SRC-family protein kinase inhibitor, and SYK-family protein kinase inhibitor. In yet other examples, the API is monovalent substituent group of at least one of an ABL1 inhibitor, BCR-ABL inhibitor, FAK inhibitor, SRC inhibitor, LYN inhibitor and SYK inhibitor.

[0019] In some examples, the API is monovalent substituent group of a serine/threonine protein kinase inhibitor. In other examples, the API is monovalent substituent group of at least one of an mitogen-activated protein kinase (MAPK)-family protein kinase inhibitor, MAP2K-family protein kinase inhibitor, MAP3K-family protein kinase inhibitor, and IκB kinase (IKK)-family protein kinase inhibitor. In still other examples, the API is monovalent substituent group of at least one of an ERK inhibitor, Jun kinase (JNK) inhibitor, p38 kinase inhibitor, MEK inhibitor, and IKK inhibitor. In yet other examples, the API is monovalent substituent group of a leucine-rich repeat kinase inhibitor.

[0020] In some examples, the API is monovalent substituent group of a leucine-rich repeat kinase (LRRK)2 inhibitor. In other examples, the API is monovalent substituent group of a protein phosphatase inhibitor. In still other examples, the API is monovalent substituent group of a calcineurin inhibitor.

[0021] In the compounds of the formulae (I), (IV), and (V), LG is a divalent substituent group formed from an amino aldehyde. Examples of suitable amino aldehydes include compounds of the formula (II):

$$H_2N—R^1—C(=O)H$$

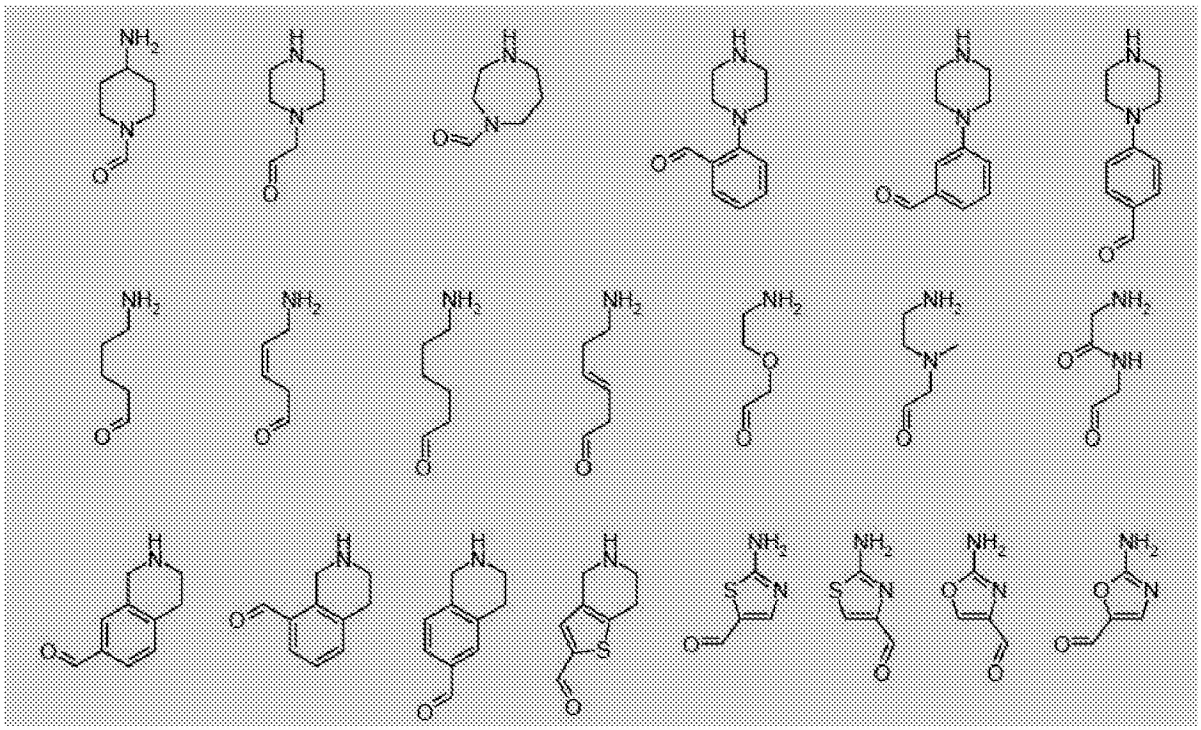
(II)

wherein,

R^1 is a divalent substituent group of a hydrocarbon;

wherein the hydrocarbon is optionally substituted and optionally interrupted.

[0022] In some embodiments, LG is a divalent substituent group formed from an amino aldehyde, illustrated below



[0023] In some embodiments, LG is a divalent substituent group formed from a compound of formula (III):

$$R^2\text{—}C(=O)H \qquad \text{(III)}$$

wherein,

R^2 is a monovalent substituent group of a nitrogen-containing heterocyle, a monovalent substituent group of a nitrogen-containing heteroaryl, or a monovalent substituent group of a nitrogen-containing hydrocarbon;

wherein the hydrocarbon is optionally substituted and optionally interrupted.

[0024] In some embodiments, LG is a divalent substituent group formed from an amino aldehyde, wherein the amino group, NH or NH_2, and the aldehyde group, C(=O)H, is separated from one another by about 200 pm to about 1,500 pm. In other embodiments, LG is a divalent substituent group, such that API and ESM are separated from one another by about 300 pm to about 2,000 pm.

[0025] In some embodiments, each of LG–ESM and LG–API independently comprise linkages, such that the functional groups that provide such linkages are selected from a combination of one of (a) and one of (b):

(a) aldehyde, isocyanate, isothiocyanate, halogen, sulfonic acid, sulfonic acid chloride, carboxylic acid, carboxylic acid chloride, hydroxyl, and protected hydroxyl;

(b) alkylhalogenide, thiol, hydroxyl, acetylene, boronic acid, and amine.

[0026] In some embodiments, ESM is a substrate of human carboxylesterase-1. Non-limiting examples of ESM groups include a monovalent substituent group of at least one of α-naphthyl ester (e.g., acetate, propionate, butyrate, valerate, caproate, caprylate, caprate, laurate, myristate, palmitate, stearate, or nonanoate), naphthol AS ester (e.g., acetate, propionate, nonanoate, phenyl acetate, phenyl propionate, phenyl butyrate, AS-D acetate, or AS-LC acetate), and naphthol AS chloroacyl ester (e.g., AS-D chloroacetate, AS β-chloropropionate, naphthol AS Ɛ-aminocaproate HBr, indoxyl acetate, or 5-bromo-indoxyl acetate), 4-nitrophenyl acetate, 4-methylumbelliferyl acetate, naphthol AS-D chloroacetate, 5-bromo-4-chloro-3-indolyl acetate, 3,6-diacetoxyphthalonitrile, 5(6)-carboxy-2',7'-dichlorofluorescein diacetate, 1-naphthyl propionate, 4-methylumbelliferyl butyrate, N-acetyl-DL-β-phenylalanine, DL-α-palmitin, 3-(2-benzoxazolyl)umbelliferyl acetate, 5-bromo-4-chloro-3-indolyl acetate, 8-butyryloxypyrene-1,3,6-trisulfonic acid trisodium salt, fluorescein dilaurate, indoxyl acetate, 4-methylumbelliferyl acetate, 4-methylumbelliferyl butyrate, naphthol AS-D chloroacetate, naphthol AS-D chloroacetate, 1-naphthyl acetate, 1-naphthyl butyrate, 4-nitrophenyl dodecanoate, 4-nitrophenyl myristate, 4-nitrophenyl octanoate, 8-octanoyloxypyrene-1,3,6-trisulfonic acid trisodium salt, paraoxon-ethyl, resorufin acetate, and a 7uinolon-protected 5-phenyl-3-hydroxypyrrolyl L-lactate substrate.

[0027] Embodiments also include pharmaceutical compositions comprising a compound of the formula (I), (IV) or (V) and a pharmaceutically acceptable carrier; or two or more compounds of the formulae (I), (IV), (V) or combinations thereof and a pharmaceutically acceptable carrier.

[0028] Embodiments also include methods of medical treatment comprising administering to an animal in need of such medical treatment, or at risk thereof, an effective amount a compound of the formula (I), (IV) or (V); or two or more compounds of the formulae (I), (IV), (V) or combinations thereof, for a period of time effective to treat the animal. In some examples, the animal is a human.

[0029] In some embodiments, the administration is systemic. In some embodiments, the administration occurs for a period of time of at least about 1 month; occurs for a period of time of at least about 3 months; is at least once-daily (OD); or is at least twice-daily (BID).

[0030] In some embodiments, the compound of the formula (I), (IV) or (V); or two or more compounds of the formulae (I), (IV), (V) or combinations

thereof is co-administered to the animal with one or more additional active pharmaceutical ingredients (APIs).

[0031] Values expressed in a range format should be interpreted in a flexible manner to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. For example, a range of "about 0.1% to about 5%" or "about 0.1% to 5%" should be interpreted to include not just about 0.1% to about 5%, but also the individual values (e.g., 1%, 2%, 3%, and 4%) and the sub-ranges (e.g., 0.1% to 0.5%, 1.1% to 2.2%, 3.3% to 4.4%) within the indicated range. The statement "about X to Y" has the same meaning as "about X to about Y," unless indicated otherwise. Likewise, the statement "about X, Y, or about Z" has the same meaning as "about X, about Y, or about Z," unless indicated otherwise.

[0032] Values expressed in a range format should be interpreted in a flexible manner to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. For example, a range of "about 0.1% to about 5%" or "about 0.1% to 5%" should be interpreted to include not just about 0.1% to about 5%, but also the individual values (e.g., 1%, 2%, 3%, and 4%) and the sub-ranges (e.g., 0.1% to 0.5%, 1.1% to 2.2%, 3.3% to 4.4%) within the indicated range. The statement "about X to Y" has the same meaning as "about X to about Y," unless indicated otherwise. Likewise, the statement "about X, Y, or about Z" has the same meaning as "about X, about Y, or about Z," unless indicated otherwise.

[0033] In the methods of manufacturing described herein, the steps can be carried out in any order without departing from the principles of the invention, except when a temporal or operational sequence is explicitly recited. Furthermore, specified steps can be carried out concurrently unless explicit claim language recites that they be carried out separately. For example, a claimed step of doing X and a claimed step of doing Y can be conducted simultaneously within a single operation, and the resulting process will fall within the literal scope of the claimed process.

[0034] The term "about" can allow for a degree of variability in a value or range, for example, within 10%, within 5%, or within 1% of a stated value or of a stated limit of a range.

[0035] The compounds of the invention exclude compounds heretofore known. With respect to the United States, the compounds or compositions herein exclude compounds that are anticipated under 35 U.S.C. §102, and that are obvious under 35 U.S.C. §103.

[0036] As used herein, "stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture. Only stable compounds are contemplated by the present invention.

[0037] Whenever a compound described herein is substituted with more than one of the same designated group (e.g., more than one of the same designated variable, substituent group, substituent, etc.), then it will be understood that each occurrence of the designated group may be the same or may be different, i.e., each designated group is "independently" selected.

[0038] The term "substituted" is intended to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. Suitable indicated groups include, e.g., alkyl, alkenyl, alkylidenyl, alkenylidenyl, alkoxy, halo, haloalkyl, 9uinolon, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, acyloxy, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, acetamido, acetoxy, acetyl, benzamido, benzenesulfinyl, benzenesulfonamido, benzenesulfonyl, benzenesulfonylamino, benzoyl, benzoylamino, benzoyloxy, benzyl, benzyloxy, benzyloxycarbonyl, benzylthio, carbamoyl, carbamate, isocyannato, sulfamoyl, sulfinamoyl, sulfino, sulfo, sulfoamino, thiosulfo, NrxRy and/or COORx, wherein each Rx and Ry are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl or 9uinolon. When a substituent is keto (i.e., =O) or thioxo (i.e., =S) group, then 2 hydrogens on the atom are replaced.

[0039] The term "monovalent" refers to an atom, ion, or chemical group with a valence of one, which thus can form one covalent bond.

[0040] The term "substituent group" (sometimes referred to as a "radical") refers to an atom, molecule, or ion that has unpaired valence electrons or an open electron shell, and therefore may be seen as having one or more "dangling" covalent bonds. A notable example of substituent group is the hydroxyl substituent group (HO−).

[0041] The term "interrupted" is intended to indicate that in between two or more adjacent carbon atoms, and the hydrogen atoms to which they are attached (e.g., methyl (CH_3), methylene (CH_2) or 10uinolo (CH)), indicated in the expression using "interrupted" is inserted with a selection from the indicated group(s), provided that the each of the indicated atoms' normal valency is not exceeded, and that the interruption results in a stable compound. Such suitable indicated groups include, e.g., with one or more non-peroxide oxy (-O-), thio (-S-), imino (-N(H)-), methylene dioxy (-OCH_2O-), carbonyl (-C(=O)-), carboxy (-C(=O)O-), carbonyldioxy (-OC(=O)O-), 10uinolone10e (-OC(=O)-), imine (C=NH), sulfinyl (SO) and sulfonyl (SO_2).

[0042] The term "alkoxy" refers to the groups alkyl-O–, where alkyl is defined herein. Preferred alkoxy groups include, e.g., methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, 1,2-dimethylbutoxy, and the like.

[0043] The term "halo" refers to fluoro, chloro, bromo, and iodo. Similarly, the term "halogen" refers to fluorine, chlorine, bromine, and iodine.

[0044] The term "trifluoromethyl" refers to the group –CF_3.

[0045] The term "hydroxyl alkyl" refers to the group HO–alkyl–.

[0046] The term "nitro" refers to the group –NO_2.

[0047] The term "cyano" refers to the group –CN.

[0048] The term "hydrogen" refers to the group –H.

[0049] As used herein, "alkyl" refers to a group derived from a straight or branched chain saturated hydrocarbon containing from one to eighteen carbon atoms. "Alkyl" can be C_1-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl (Me, –CH_3), ethyl (Et, –CH_2CH_3), 1-propyl (n-Pr, n-propyl, –$CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, –$CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, –$CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (1-Bu, i-butyl, –$CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, –$CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, –$C(CH_3)_3$), 1-pentyl (n-pentyl, –$CH_2CH_2CH_2CH_2CH_3$), 2-pentyl (–$CH(CH_3)CH_2CH_2CH_3$), 3-pentyl (–$CH(CH_2CH_3)_2$), 2-methyl-2-butyl (–$C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl (–$CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl (–$CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl (–$CH_2CH(CH_3)CH_2CH_3$), 1-hexyl (–$CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl (–$CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl (–$CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-

2-pentyl (–$C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl (–$CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl (–$CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl (–$C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl (–$CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl (–$C(CH_3)_2CH(CH_3)_2$), and 3,3-dimethyl-2-butyl (–$CH(CH_3)C(CH_3)_3$. The alkyl groups of the present invention are optionally substituted with one, two, three, four, or five substituents.

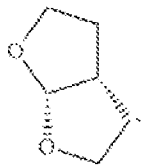
[0050] As used herein, "aryl" refers to a phenyl group, or a bicyclic fused ring system wherein one or both of the rings is a phenyl group. Bicyclic fused ring systems consist of a phenyl group fused to a four- to six-membered aromatic or non-aromatic carbocyclic ring. The aryl groups of the present invention can be attached to the parent molecular moiety through any substitutable carbon atom in the group. Representative examples of aryl groups include, but are not limited to, indanyl, indenyl, naphthyl, phenyl, and tetrahydronaphthyl. The aryl groups of the present invention are optionally substituted with one, two, three, four, or five substituents.

[0051] As used herein, "heterocycle" or "heterocyclyl" refers to a four-, five-, six-, or seven-membered ring containing one, two, three, or four heteroatoms independently selected from nitrogen, oxygen, and sulfur. The four-membered ring has zero double bonds, the five-membered ring has zero to two double bonds, and the six- and seven-membered rings have zero to three double bonds. The term "heterocyclyl" also includes bicyclic groups in which the heterocyclyl ring is fused to another monocyclic heterocyclyl group, or a four- to six-membered aromatic or non-aromatic carbocyclic ring; as well as bridged bicyclic groups such as 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oc-2-tyl, and 2-azabicyclo[2.2.2]oc-3-tyl. The heterocyclyl groups of the present invention can be attached to the parent molecular moiety through any carbon atom or nitrogen atom in the group. Examples of heterocyclyl groups include, but are not limited to, benzothienyl, furyl, imidazolyl, indolinyl, indolyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrrolopyridinyl, pyrrolyl, thiazolyl, thienyl, thiomorpholinyl, 7-azabicyclo[2.2.1]hept-7-yl, 2-azabicyclo[2.2.2]oc-2-tyl, and 2-azabicyclo[2.2.2]oc-3-tyl. The heterocycle groups of the present invention are optionally substituted with one, two, three, four, or five substituents.

[0052] "Heterocycle" includes by way of example and not limitation these heterocycles described in Paquette, Leo A.; Principles of Modern Heterocyclic Chemistry (W. A. Benjamin, N.Y., 1968), particularly Chapters 1, 3,

4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and J. Am. Chem. Soc. (1960) 82:5566. In one specific embodiment of the invention "heterocycle" includes a "carbocycle" as defined herein, wherein one or more (e.g. 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (e.g. O, N, or S).

[0053] Examples of heterocycles include by way of example and not limitation pyridyl, dihydropyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4H-carbazolyl, carbazolyl, f3-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, isatinoyl, and bis-tetrahydrofuranyl:



[0054] By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a 12uinolone or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-

pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

[0055] By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or .beta.-carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

[0056] As used herein, "cycloalkyl" refers to a saturated monocyclic, hydrocarbon ring system having three to twelve carbon atoms and zero heteroatoms. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, and cyclohexyl. The cycloalkyl groups of the present invention are optionally substituted with one, two, three, four, or five substituents.

[0057] As to any of the above groups, which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible.

[0058] The phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio.

[0059] It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine anti-fungal or

anti-bacterial activity using the standard tests described herein, or using other similar tests which are well known in the art.

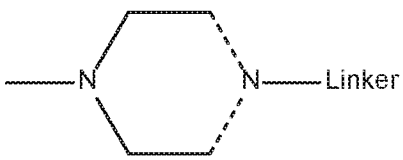
[0060] "Therapeutically effective amount" is intended to include an amount of a compound described herein, or an amount of the combination of compounds described herein, e.g., to treat or prevent the disease or disorder, or to treat the symptoms of the disease or disorder, in a host. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, Adv. Enzyme Regul., 22:27 (1984), occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased activity, or some other beneficial effect of the combination compared with the individual components.

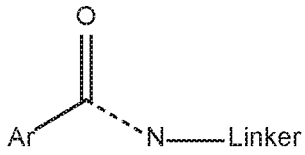
[0061] As used herein, "treating" or "treat" includes: (i) preventing a pathologic condition from occurring (e.g. prophylaxis); (ii) inhibiting the pathologic condition or arresting its development; (iii) relieving the pathologic condition; and/or (iv) diminishing symptoms associated with the pathologic condition.

[0062] The term "in vitro" refers to activities that are conducted using components of an organism that have been isolated from their usual biological surroundings in order to permit a more detailed or more convenient analysis than can be done with whole organisms.

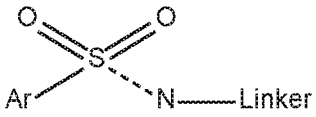
[0063] The term "in vivo" refers to activities using a whole, living organism as opposed to a partial or dead organism.

[0064] Representative compounds of the present invention can generally be prepared, as outlined in the general synthetic schemes below. In reference to the compounds of the invention illustrated in Table A, the API–LG moiety can fall within any one of the following 7 classes of compounds:

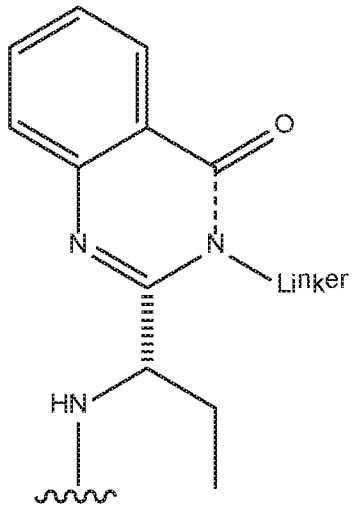
1. R–CH_2 --- N–Linker
2. Ar --- N–Linker
3. 



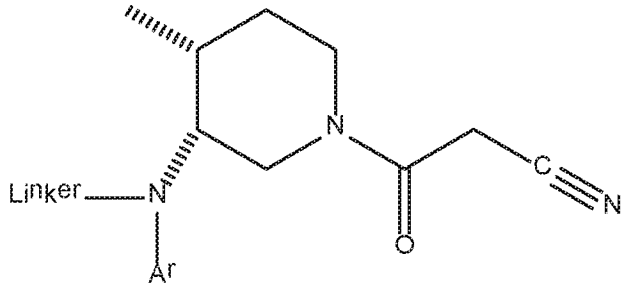
4. Ar = Aromatic or heteroarometric ring.



5. Ar = Aromatic or heteroarometric ring.



6.

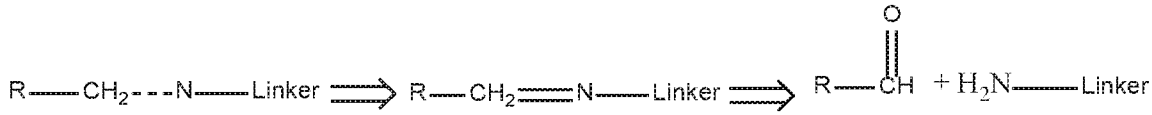


7. Ar = Aromatic or heteroarometric ring.

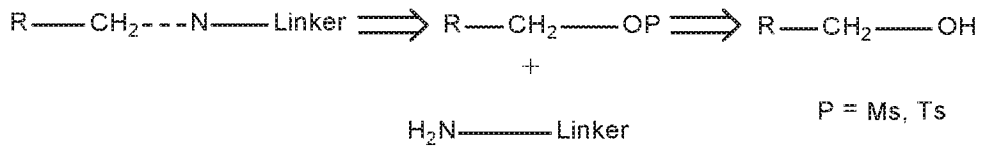
[0065] The compounds illustrated in Table A are designated by the 7 classes (see the compounds in Table A, column API–LG, Active Fragment Point of attachment for linker). These 7 classes of compounds can generally be prepared, as outlined in the general synthetic schemes below.

1. R——CH_2---N——Linker

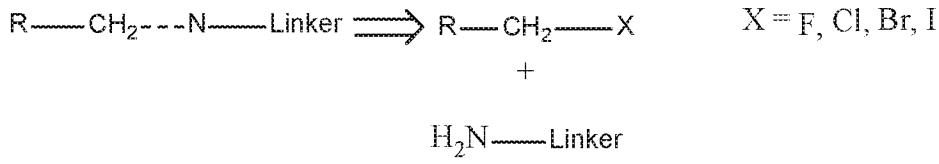
(A)



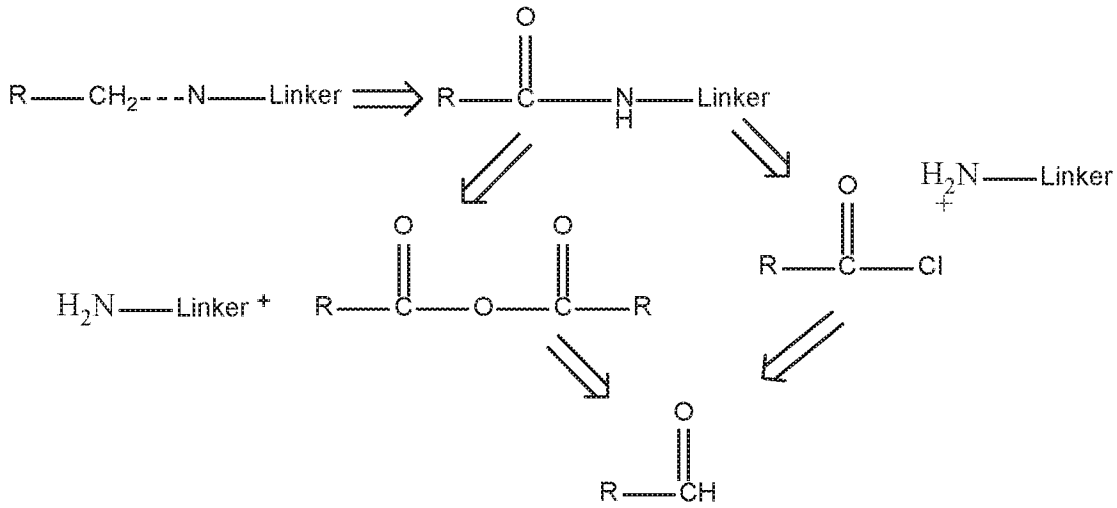
(B)



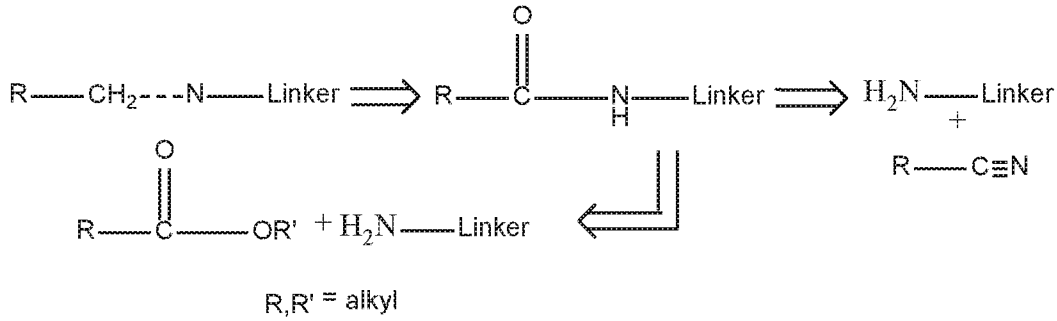
I



(D)

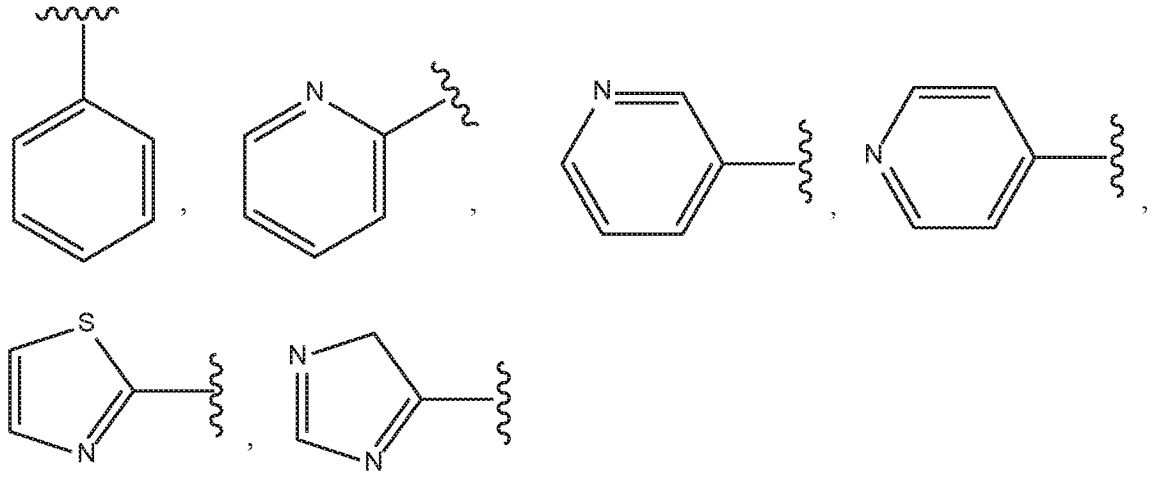


I

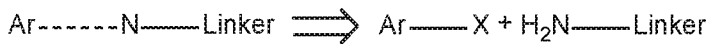


2. Ar------N—Linker

Ar = Aromatic or heteroaromatic ring, e.g.,



(A)

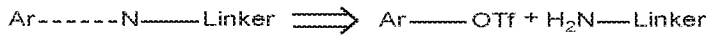


X = F, Cl, Br, I

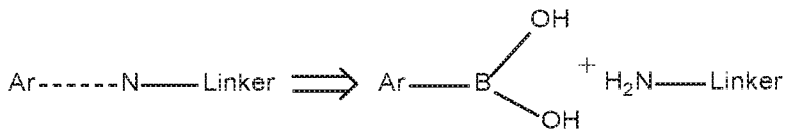
(B)



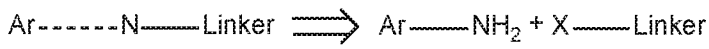
I



(D)

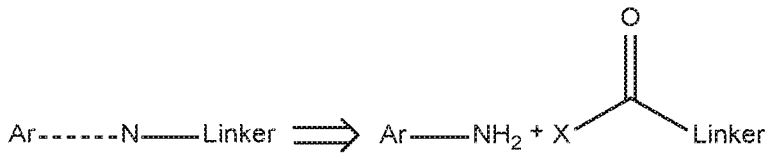


I

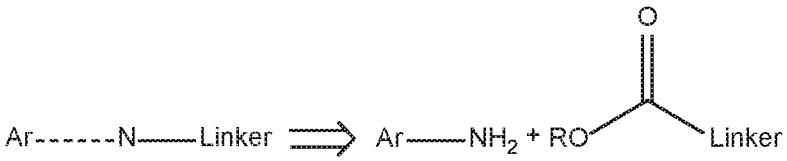


X = F, Cl, Br, I

(F)



(G)

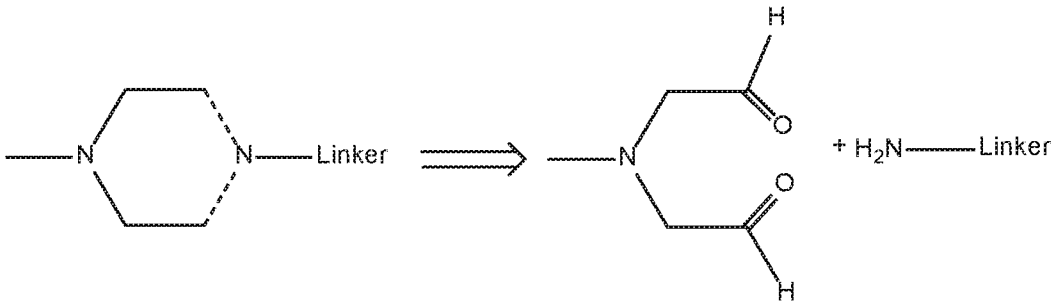


R = alkyl

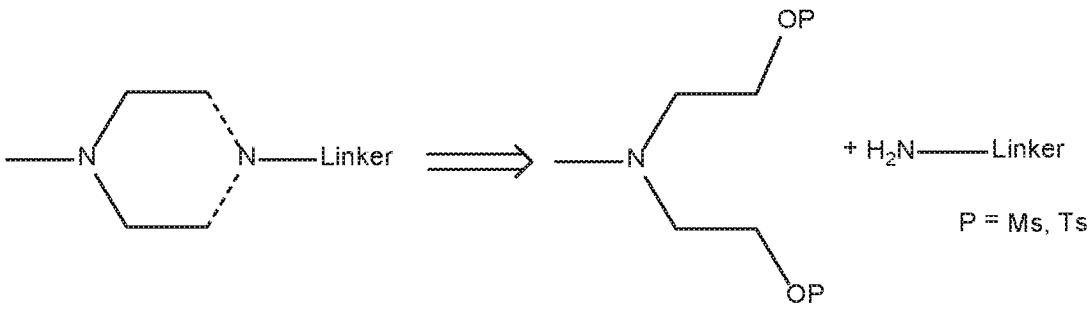


3.

(A)

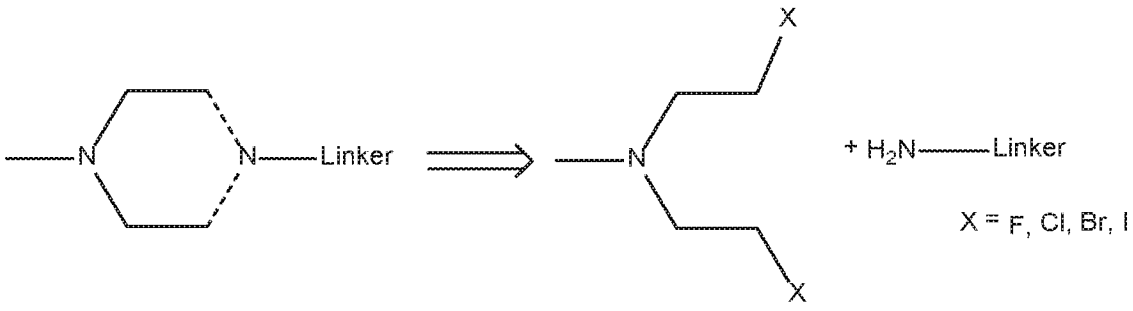


(B)



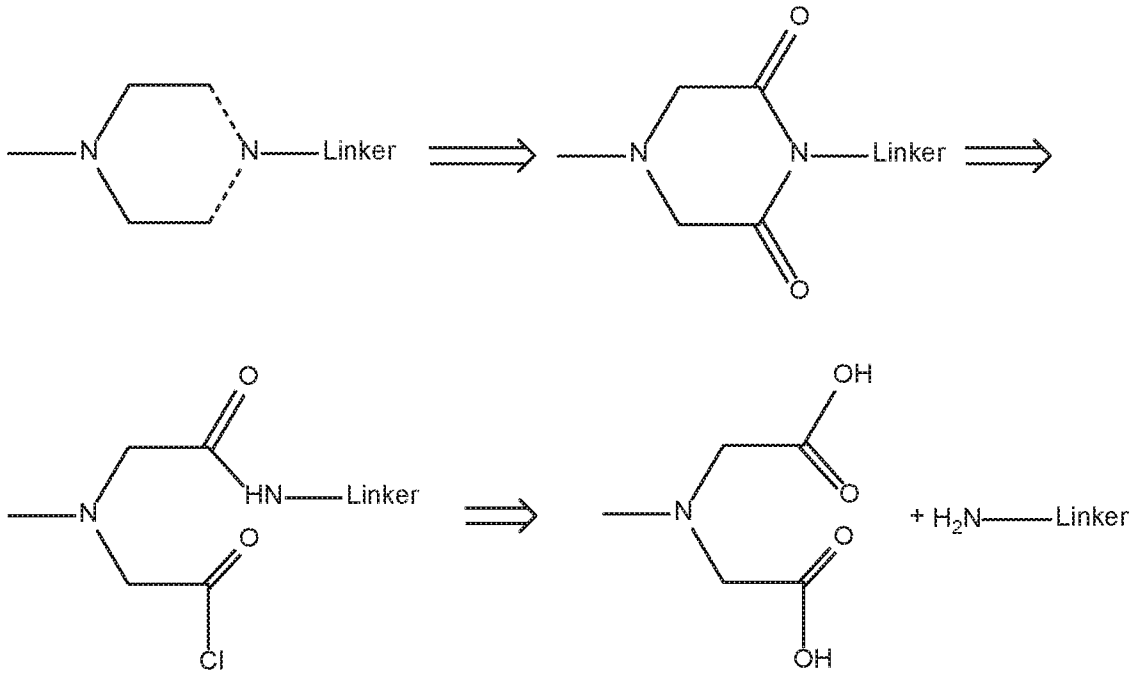
P = Ms, Ts

I



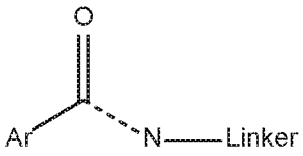
X = F, Cl, Br, I

(D)



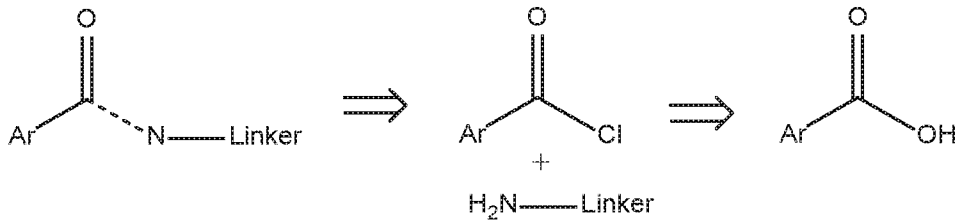
(or)

(anhydride)

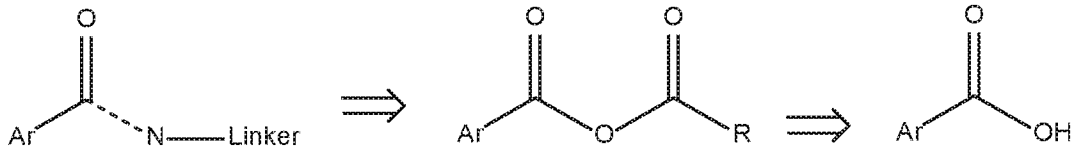


4. Ar = Aromatic or heteroarometric ring.

(A)



(B)

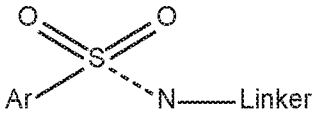


(anhydride)

+

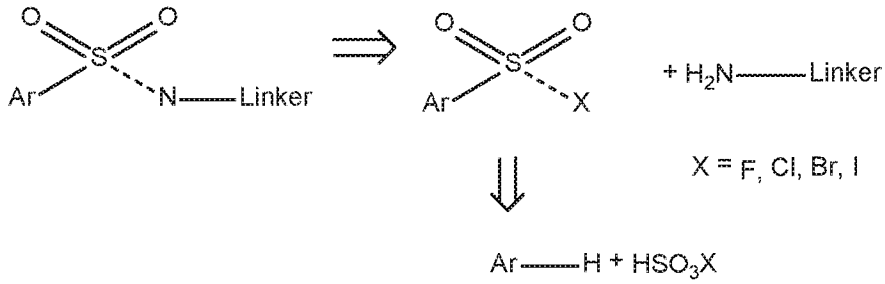
H_2N——Linker

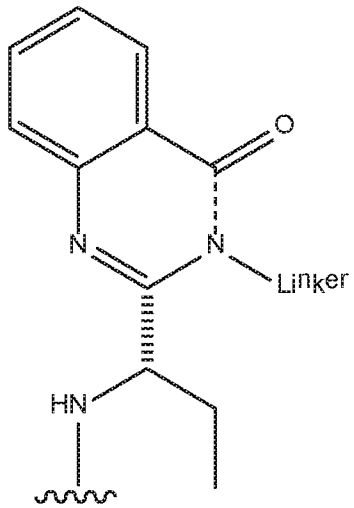
R = alkyl



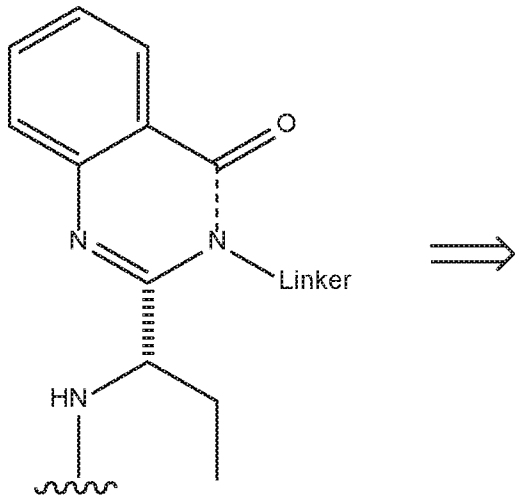
5. Ar = Aromatic or heteroarometric ring.

(A)

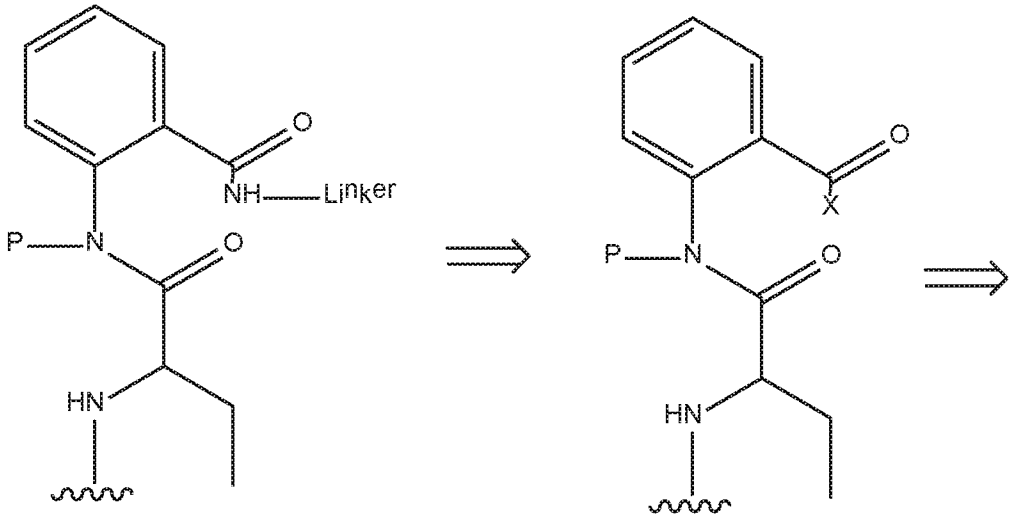




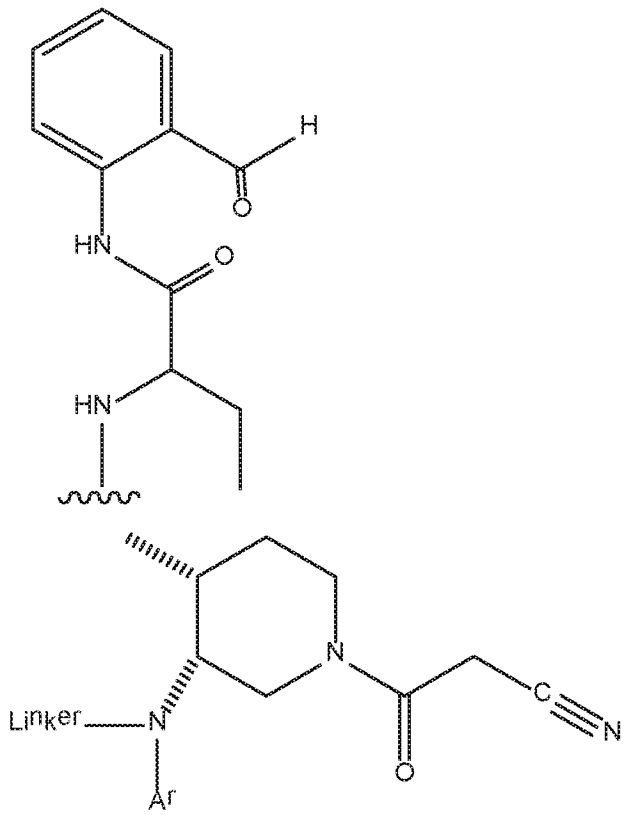
6.



5

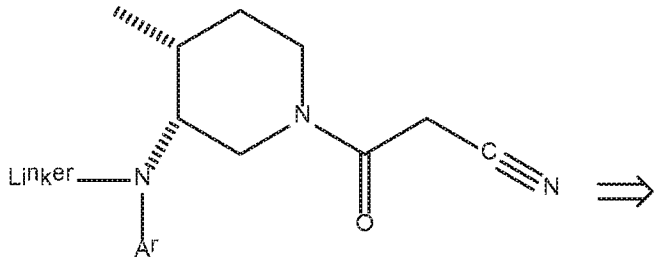


P = Protecting gp., e.g., "Boc"

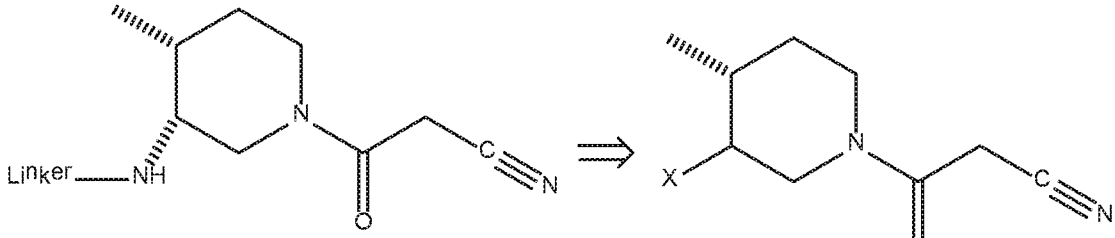


Ar = Aromatic or heteroaromatic ring

7.



Ar = Aromatic or heteroaromatic ring



\+

Ar—X

(See #2)

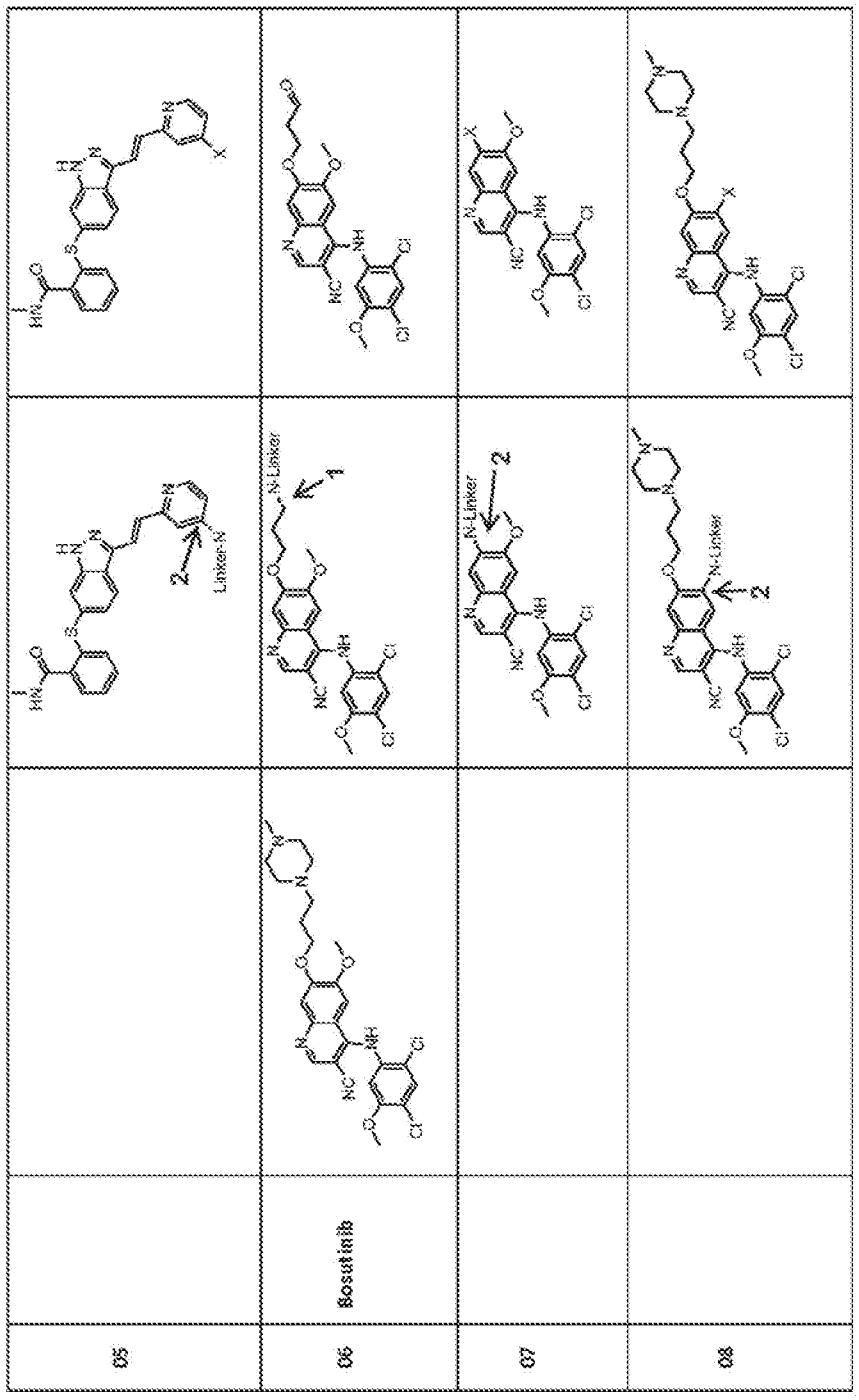
X = F, Cl, Br, I

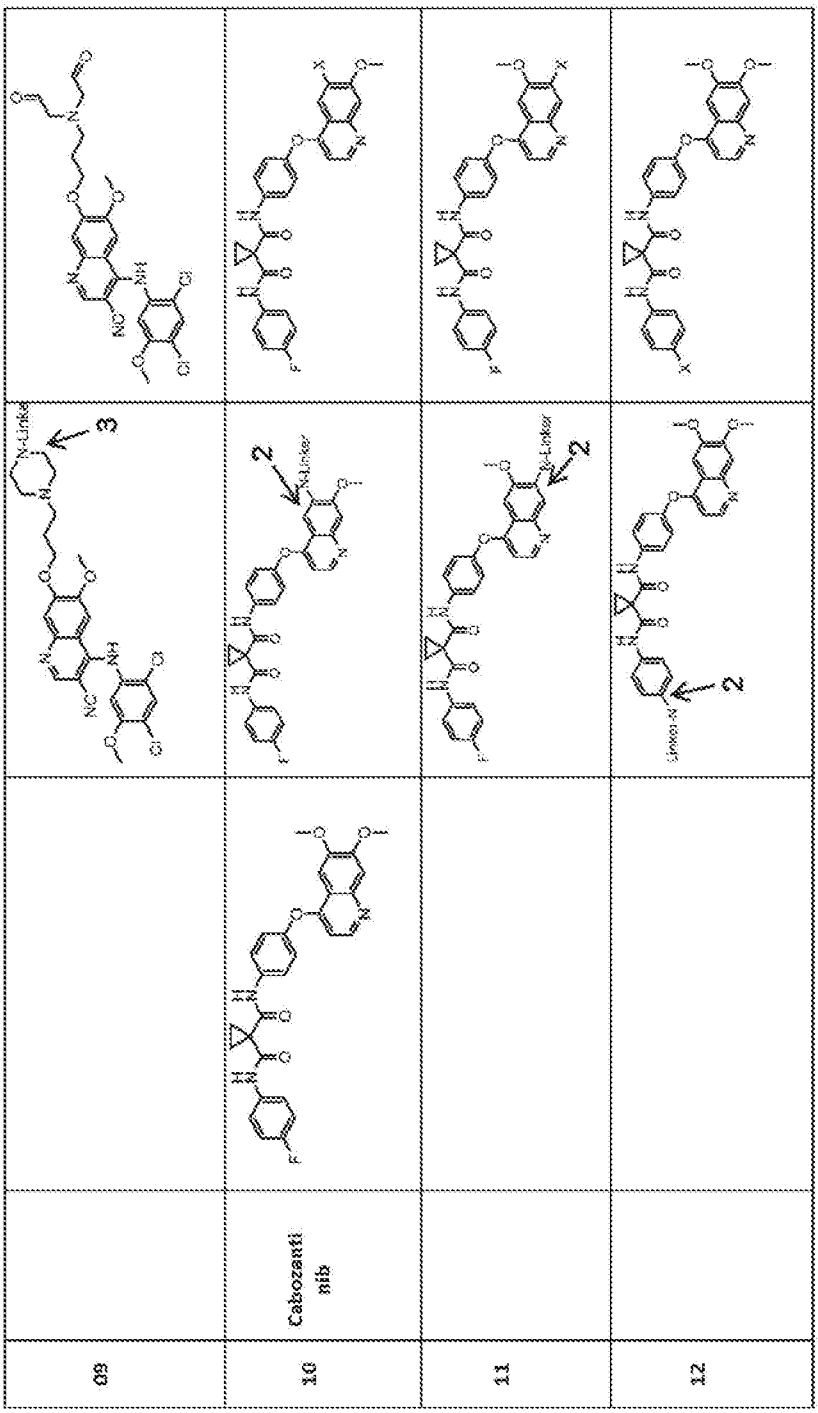
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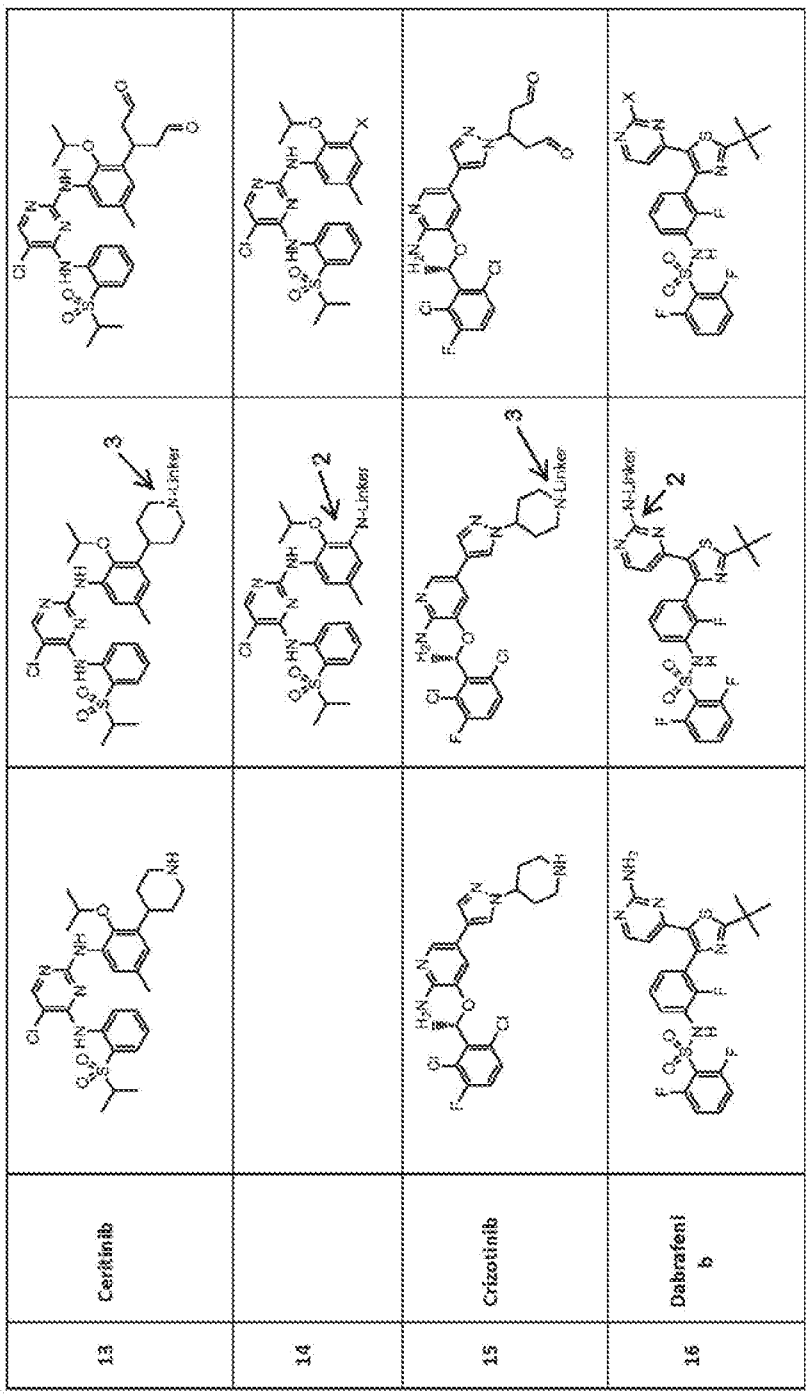
H_2N—Linker

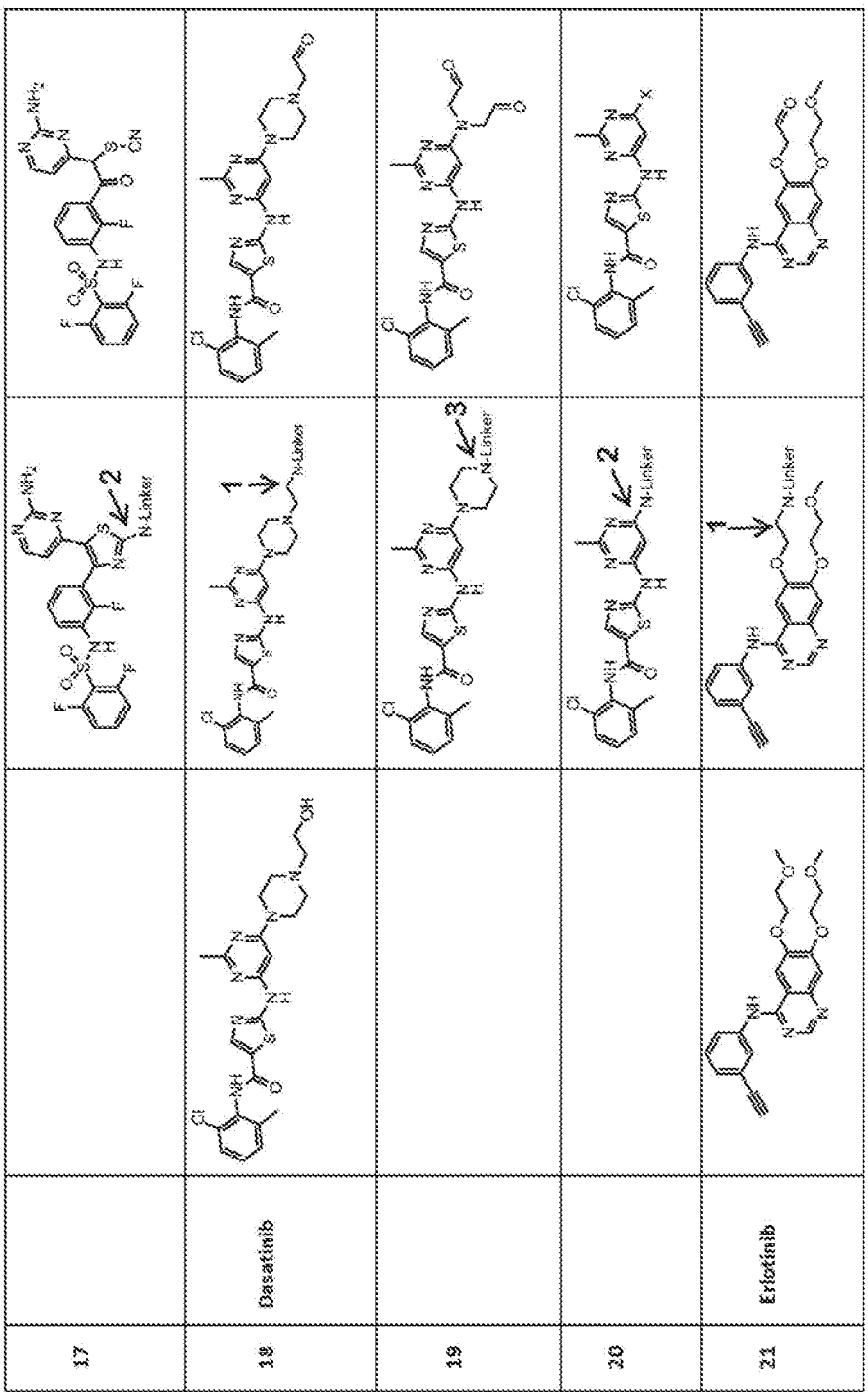
Table A

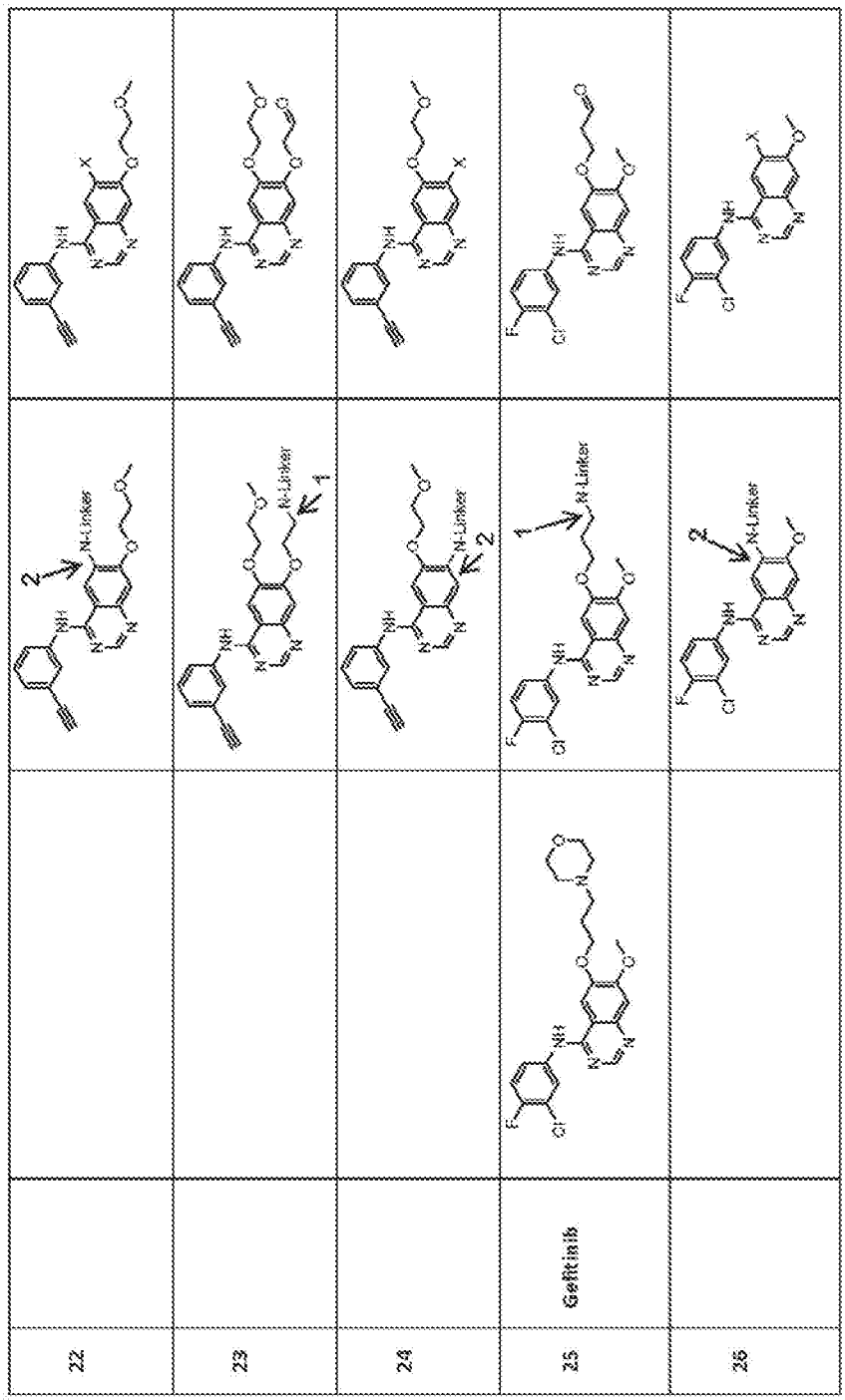
#	Kinase Inhibitor	Structure (API)	API-LG (Active Fragment Point of Attachment for Linker)	Starting Molecule (Building Block)
01	Afatinib			
02				
03	Axitinib			
04				

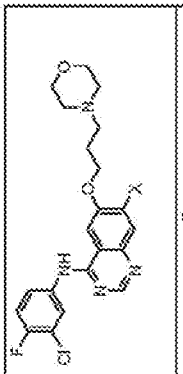
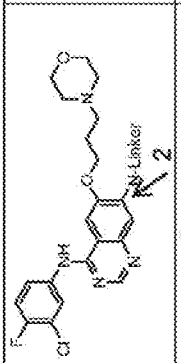
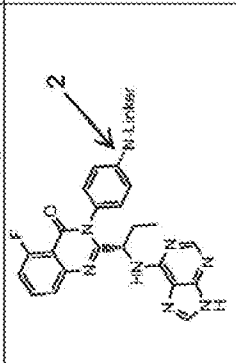
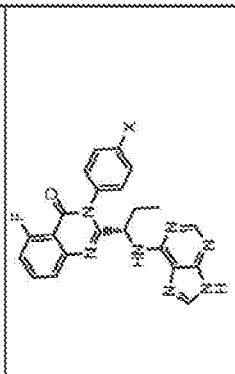
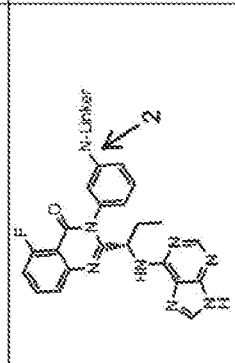
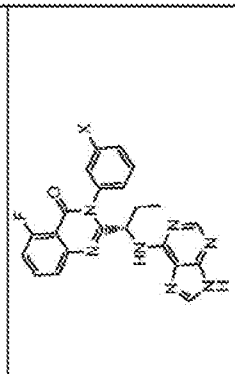
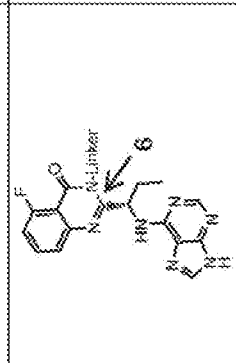
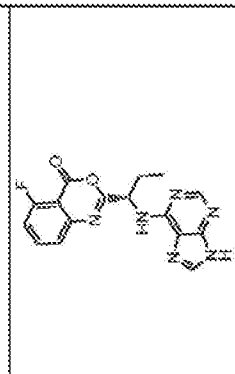

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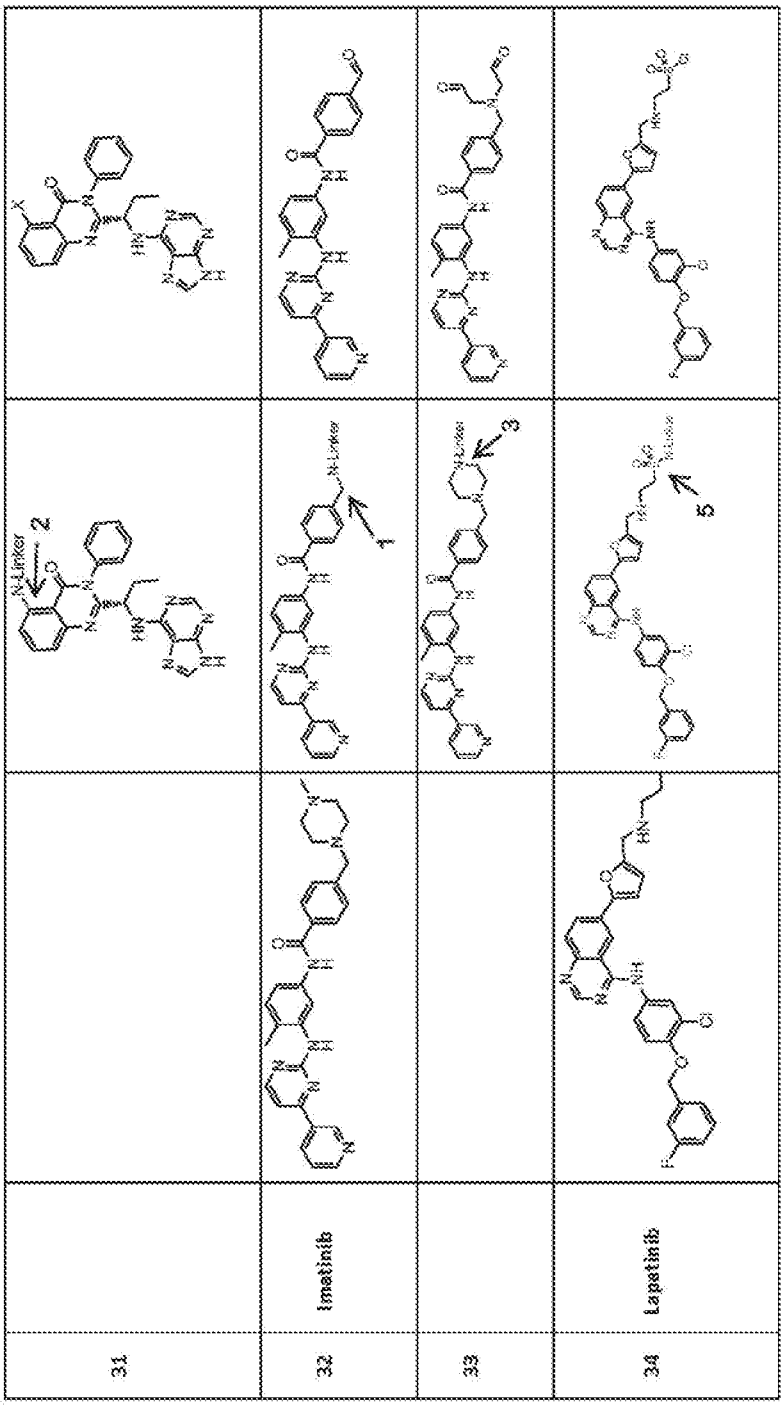

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Cabozantinib
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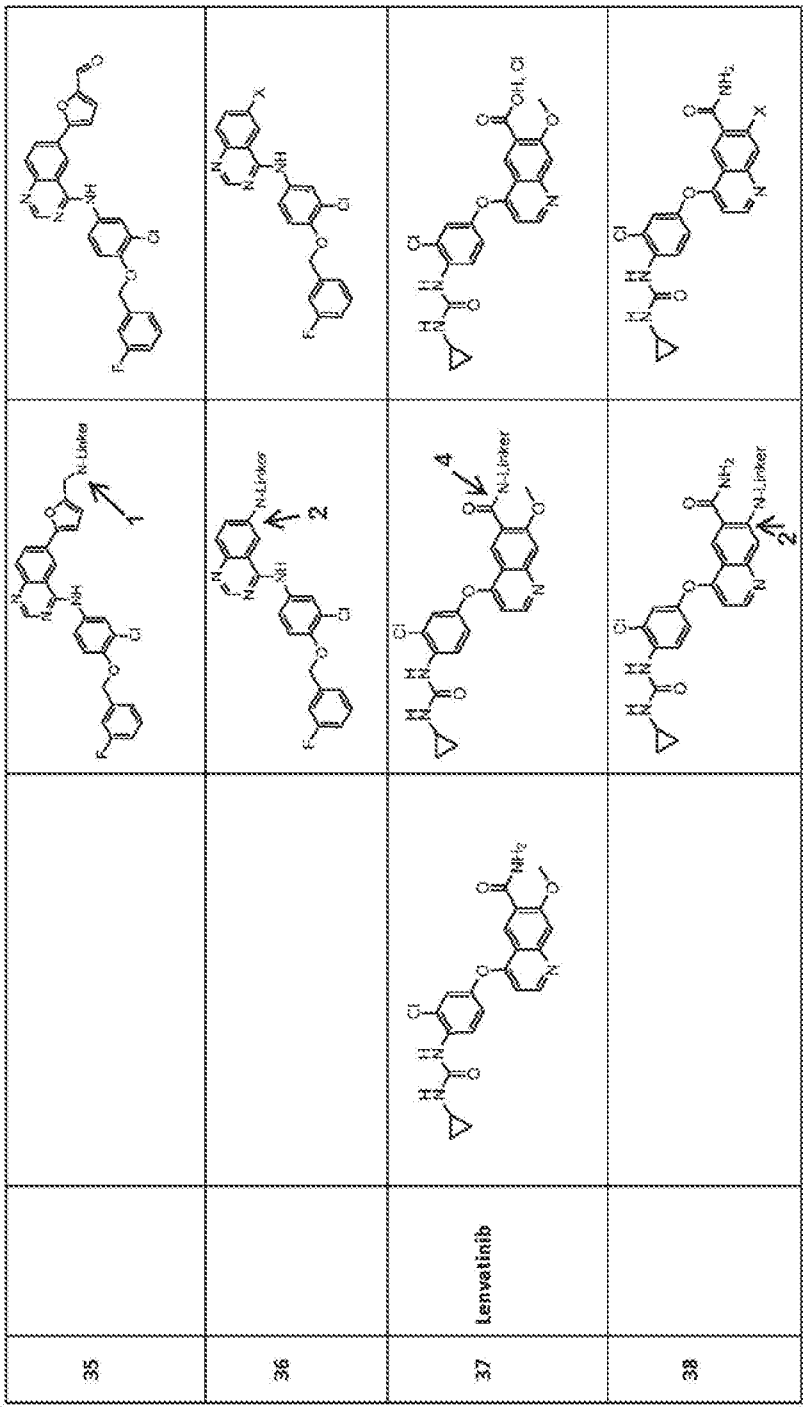

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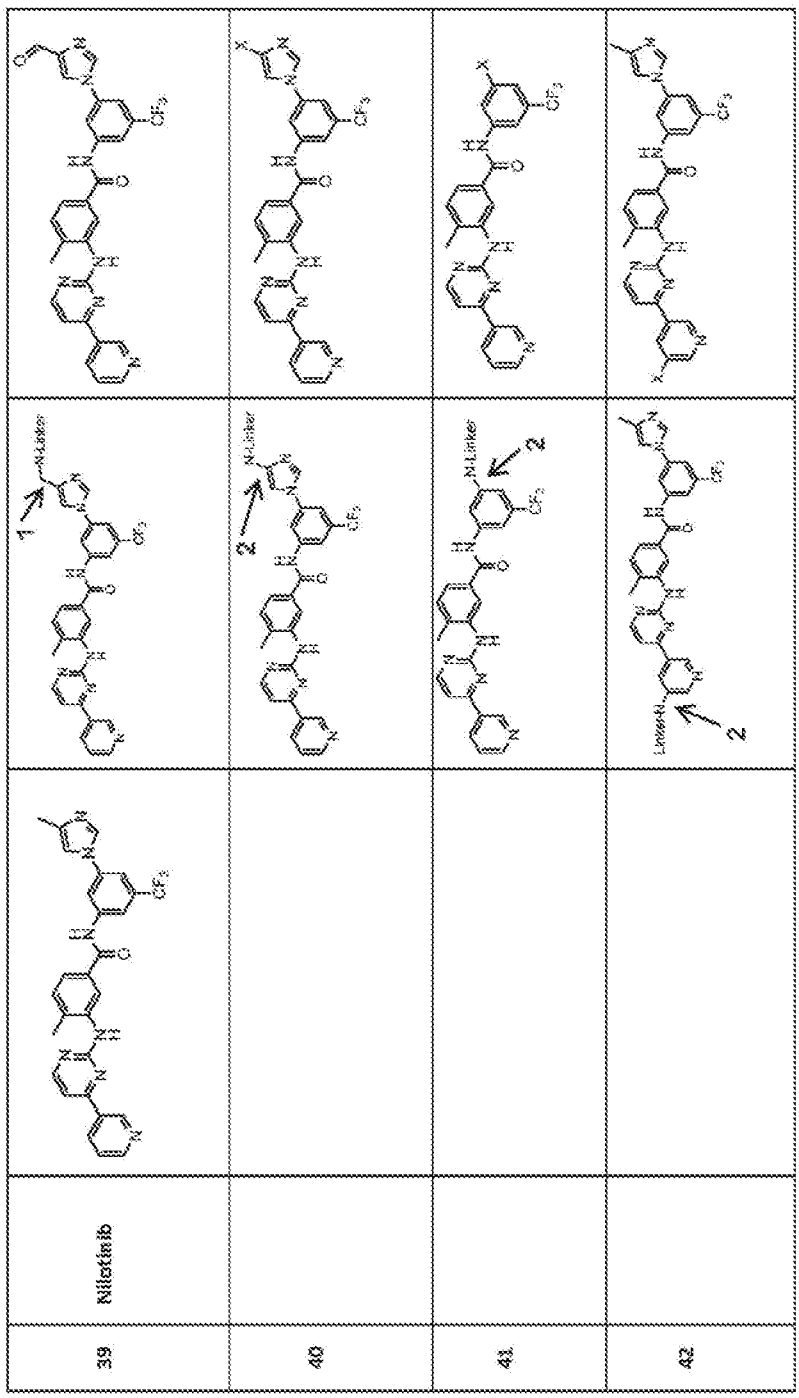

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Gefitinib
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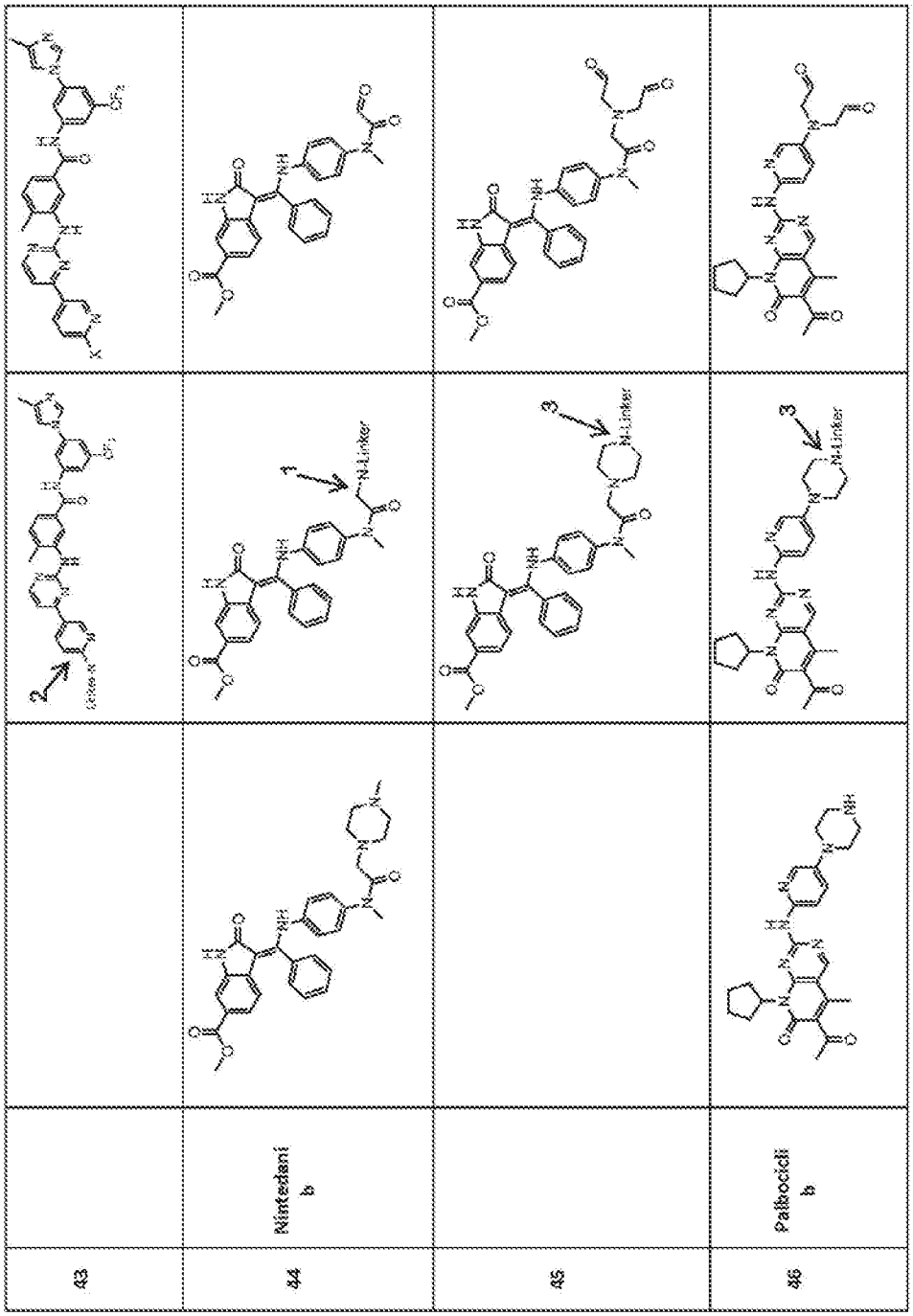
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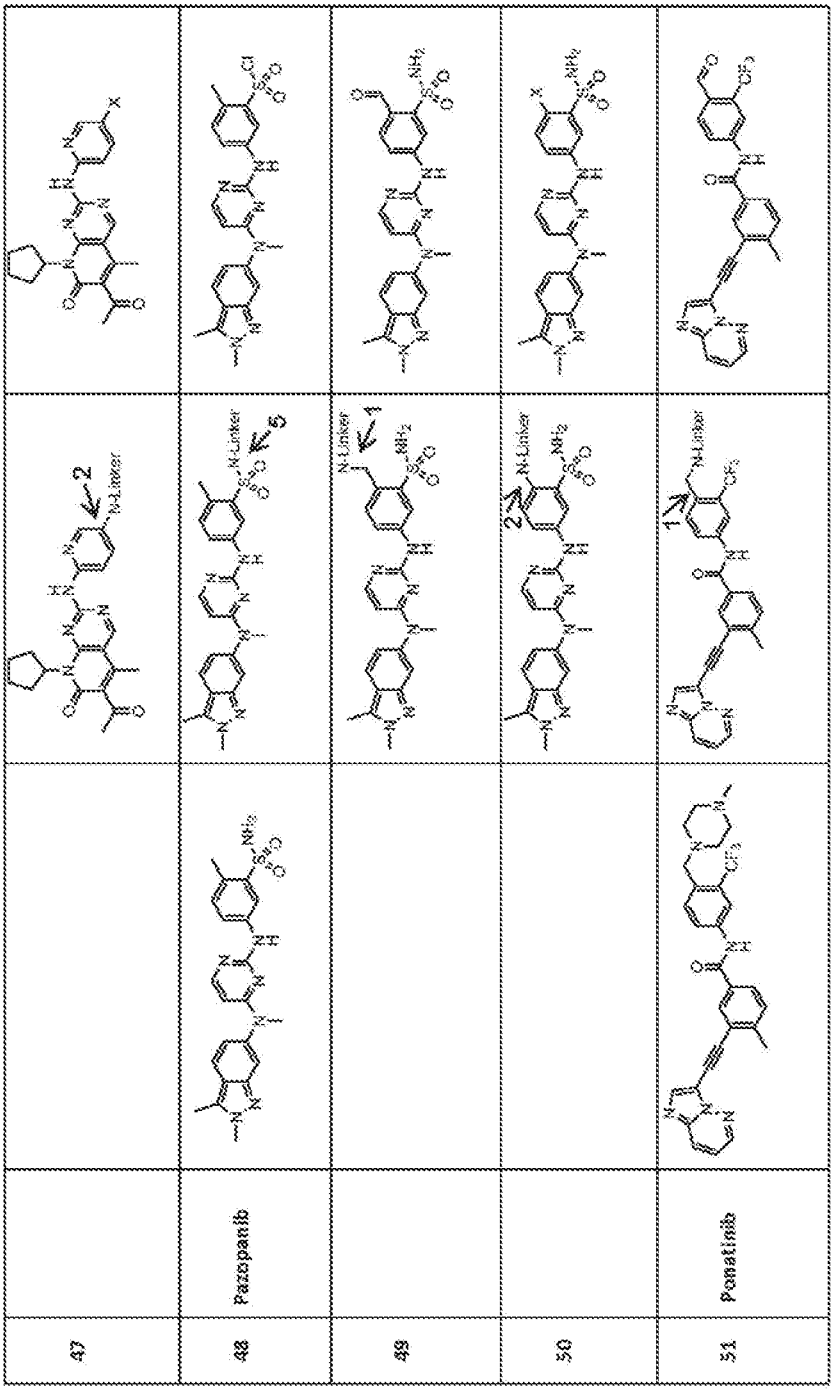

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Lapatinib
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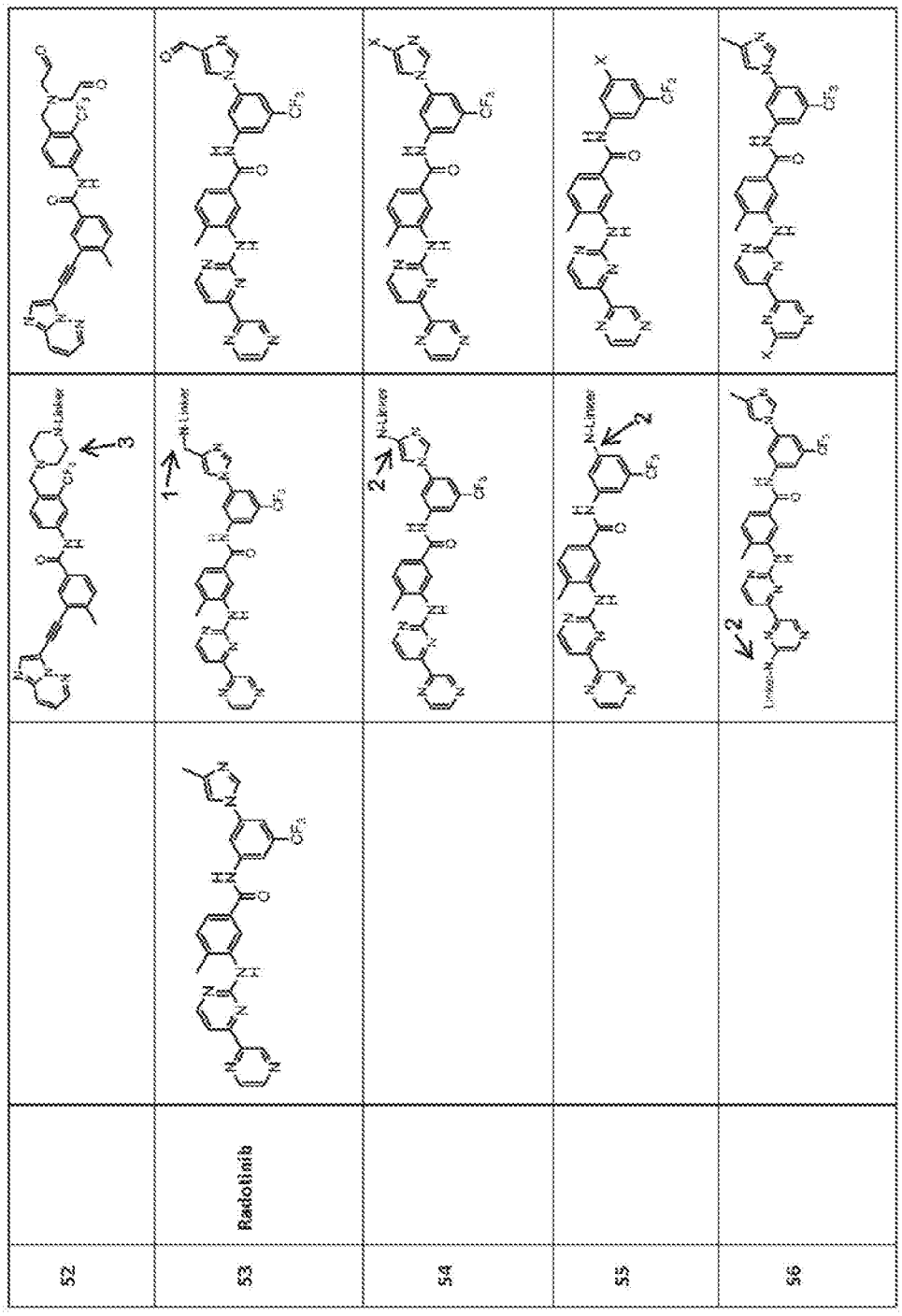

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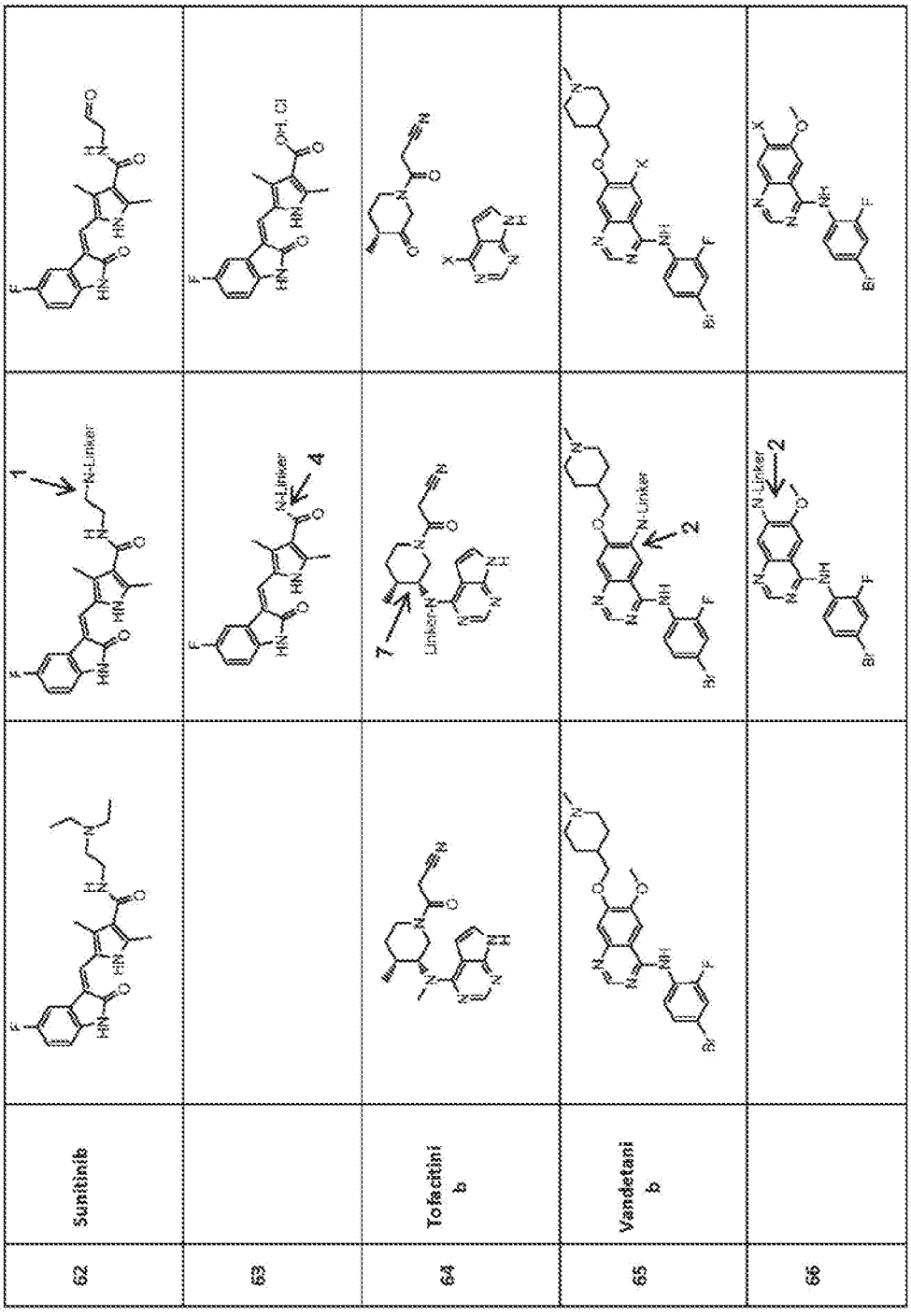
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Pazopanib
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Radotinib

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58	Regorafenib			
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60	Sorafenib			
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Tofacitini b
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68	Vemurafenib		

X=F, Cl, Br, I

Methods of Manufacturing

[0066] The compounds of the invention can be prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art. However, many of the known techniques are elaborated in Compendium of Organic Synthetic Methods (John Wiley & Sons, New York) Vol. 1, Ian T. Harrison and Shuyen Harrison (1971); Vol. 2, Ian T. Harrison and Shuyen Harrison (1974); Vol. 3, Louis S. Hegedus and Leroy Wade (1977); Vol. 4, Leroy G. Wade Jr., (1980); Vol. 5, Leroy G. Wade Jr. (1984); and Vol. 6, Michael B. Smith; as well as March, J., Advanced Organic Chemistry, 3rd Edition, John Wiley & Sons, New York (1985); Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry, In 9 Volumes, Barry M. Trost, Editor-in-Chief, Pergamon Press, New York (1993); Advanced Organic Chemistry, Part B: Reactions and Synthesis, 4th Ed.; Carey and Sundberg; Kluwer Academic/Plenum Publishers: New York (2001); Advanced Organic Chemistry, Reactions, Mechanisms , and Structure, 2nd Edition, March, McGraw Hill (1977); Protecting Groups in Organic Synthesis, 2nd Edition, Greene, T.W., and Wutz, P.G.M., John Wiley & Sons, New York (1991); and Comprehensive Organic Transformations, 2nd Edition, Larock, R.C., John Wiley & Sons, New York (1999).

[0067] Further description for the methods of preparing the compounds described herein can be found in the examples herein.

[0068] The compounds described herein can be purified utilizing standard, well-known purification techniques of organic synthesis. Such purification techniques include, e.g., sublimation, crystallization, filtration, extraction (e.g., liquid-liquid extraction or solid-liquid extraction), distillation (e.g., fractional distillation), and chromatography (e.g., high pressure liquid chromatography (HPLC)).

Pharmaceutical Formulations

[0069] The compounds described herein can be formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets can contain excipients, glidants, fillers, binders and the like. Aqueous formulations can be prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations can optionally contain excipients such as those set forth in the Handbook of Pharmaceutical Excipients, 5th Ed.; Rowe, Sheskey, and Owen, Eds.; American Pharmacists Association; Pharmaceutical Press: Washington,

DC, 2006. Excipients can include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations can range from about 3 to about 11, but will ordinarily be about 7 to 10.

[0070] While it is possible for the compounds described herein to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, include at least one compound described herein, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

[0071] The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, (1985). Such methods include the step of bringing into association the compound described herein with the carrier, which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the compound described herein, with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0072] Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the compound described herein; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The compound described herein may also be administered as a bolus, electuary or paste.

[0073] A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the compound described herein in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound described herein moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so

as to provide slow or controlled release of the compound described herein therefrom.

[0074] For administration to the eye or other external tissues e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the compound(s) described herein in an amount of, for example, 0.075 to 20% w/w (including compound(s) described herein in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the compound(s) described herein may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the compound(s) described herein may be formulated in a cream with an oil-in-water cream base.

[0075] If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the compound(s) described herein through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

[0076] The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

[0077] Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

[0078] The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to

avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

[0079] Pharmaceutical formulations according to the present invention include one or more compounds described herein with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the compound(s) described herein may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the compound(s) described herein in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[0080] Formulations for oral use may be also presented as hard gelatin capsules where the compound described herein is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules

wherein the compound described herein is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

[0081] Aqueous suspensions of the invention contain the compound(s) described herein in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

[0082] Oil suspensions may be formulated by suspending the compound(s) described herein in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

[0083] Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the compound(s) described herein in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0084] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol

anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

[0085] The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

[0086] The amount of compound(s) described herein that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1500 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the compound(s) described herein per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

[0087] Formulations suitable for administration to the eye include eye drops wherein the compound described herein is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the compound(s) described herein. The compound described herein is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

[0088] Formulations suitable for topical administration in the mouth include lozenges comprising the compound(s) described herein in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the compound(s) described herein in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the compound(s) described herein in a suitable liquid carrier.

[0089] Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

[0090] Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the compound(s) described herein. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of a given condition.

[0091] Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the compound(s) described herein such carriers as are known in the art to be appropriate.

[0092] Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

[0093] The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as

herein above recited, or an appropriate fraction thereof, of the compound(s) described herein.

[0094] It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[0095] The invention further provides veterinary compositions comprising at least one compound described herein as above defined together with a veterinary carrier therefor.

[0096] Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the compound(s) described herein. These veterinary compositions may be administered orally, parenterally or by any other desired route.

[0097] Compounds of the invention can also be formulated to provide controlled release of the compound(s) described herein to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the compound(s) described herein. Accordingly, the invention also provided compositions comprising one or more compounds of the invention formulated for sustained or controlled release.

[0098] Effective dose of the compound(s) described herein depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses), the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about .01 to about 5 mg/kg body weight per day. More typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1500 mg, preferably between 5 mg and 1000 mg, and may take the form of single or multiple doses.

Routes of Administration

[0099] One or more compounds of the invention (herein referred to as the compound(s) described herein) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including

subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. One advantage of the compounds of this invention is that in specific embodiments, the compounds are orally bioavailable and may be dosed orally.

Combination Therapy

[00100] Compound(s) described herein can also be used in combination with other active ingredients. Such combinations are selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination.

[00101] It is also possible to combine any compound described herein with one or more other active ingredients in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

[00102] The combination therapy may provide "synergy" and "synergistic effect", i.e. the effect achieved when the compounds used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the compounds are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g., in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each compound described herein is administered sequentially, i.e. serially, whereas in combination therapy, effective dosages of two or more compounds described herein are administered together.

[00103] Pharmaceutical kits useful in the present invention, which include a therapeutically effective amount of a pharmaceutical composition that includes a compound of component (a) and one or more compounds of component (b), in one or more sterile containers, are also within the ambit of the present invention. Sterilization of the container may be carried out using conventional sterilization methodology well known to those skilled in the art. Component (a) and component (b) may be in the same sterile container or in separate sterile containers. The sterile containers or materials may include separate containers,

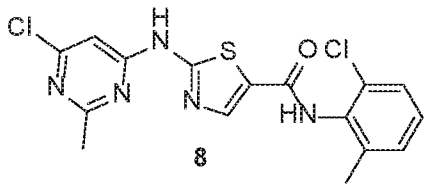
or one or more multi-part containers, as desired. Component (a) and component (b), may be separate, or physically combined into a single dosage form or unit as described above. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as for example, one or more pharmaceutically acceptable carriers, additional vials for mixing the components, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit.

[00104] All publications, patents, and published patent applications disclosed herein are incorporated herein by reference in their entirety. While in the foregoing specification this invention (as defined by the issued claims) invention has been described in relation to certain preferred embodiments thereof, and many details have been set forth for purposes of illustration, it will be apparent to those skilled in the art that the invention is susceptible to additional embodiments and that certain of the details described herein may be varied considerably without departing from the basic principles of the invention.

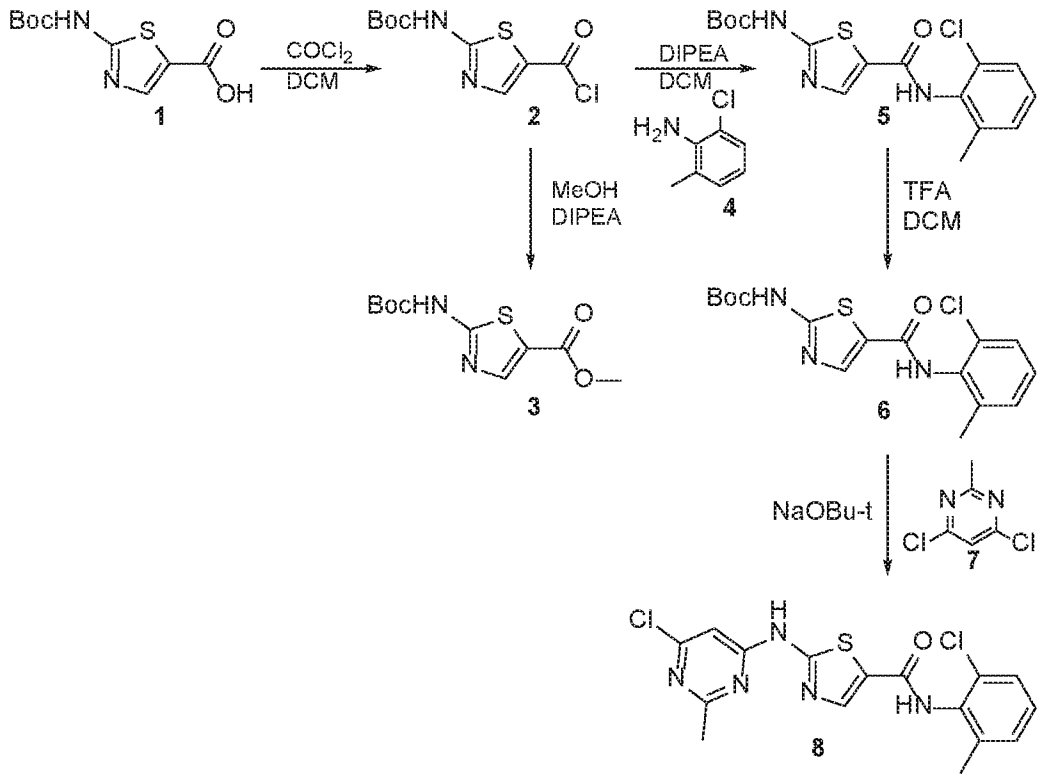
Examples

[00105] The present invention can be better understood by reference to the following examples which are offered by way of illustration. The present invention is not limited to the examples given herein.

Example 1: Synthesis of compound 8



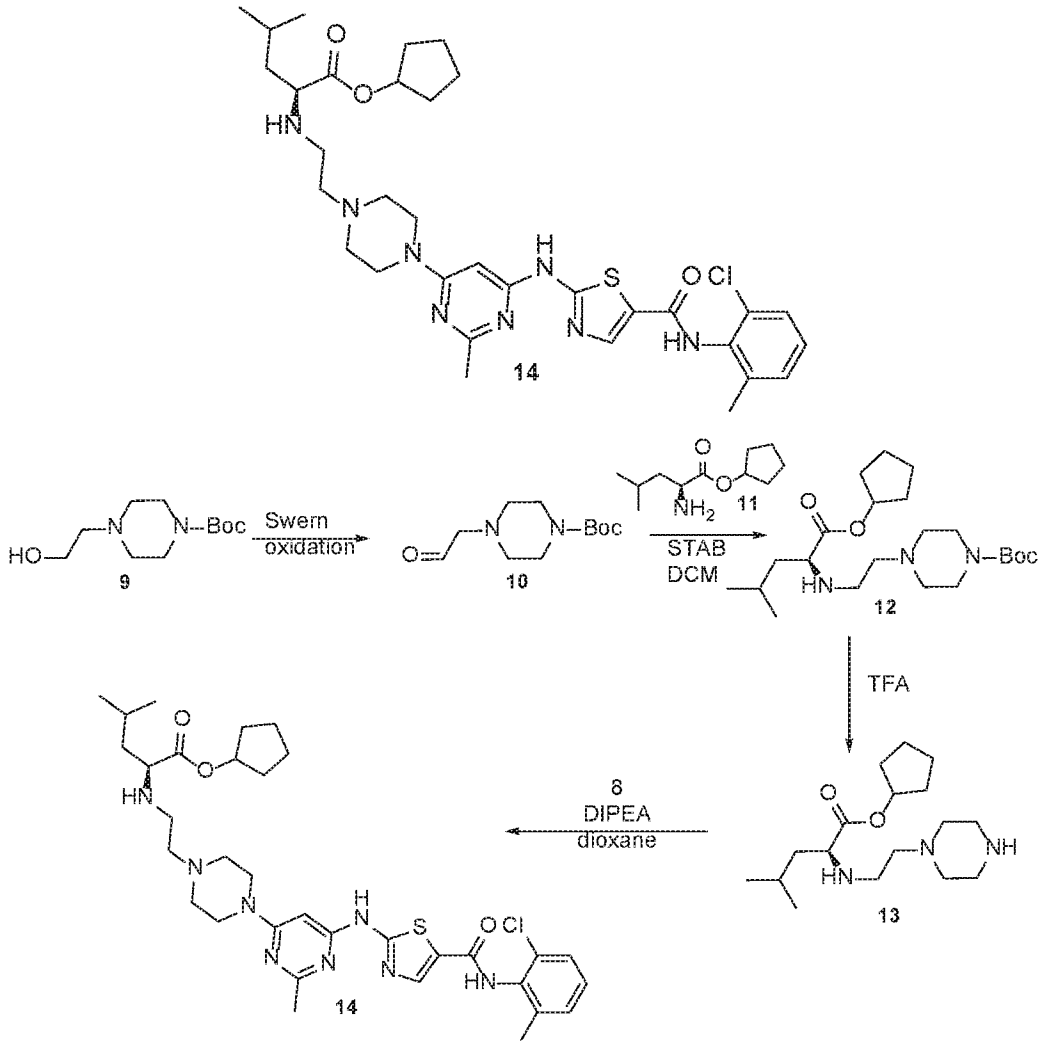
8



Scheme 1

[00106] Compound 8 was made using by adapting the synthesis disclosed in *J.Med.Chem.* 2006, 6819. Synthesis of amide 5 was accomplished in two steps, starting from compound 1. Compound 1 was converted to acid chloride 2 using oxalyl chloride in dichloromethane (DCM). Formation of the acid chloride was confirmed by quenching an aliquot in methanol (MeOH); LCMS analysis indicated the presence of the corresponding methyl ester 3 in >90%. Addition of 2 to a mixture of excess aniline 4 and diisopropyl ethylamine (DIPEA) gave good conversion to amine 5. After filtering the solids off this afforded 1.15 g (40%) amide 5 in high purity. Removal of the Boc-group using trifluoroacetic acid (TFA) gave good conversion to amine 6. Amine 6 was converted to compound 8 in the presence of compound 7 and sodium t-butoxide (NaOBu-t).

Example 2: Synthesis of compound 14

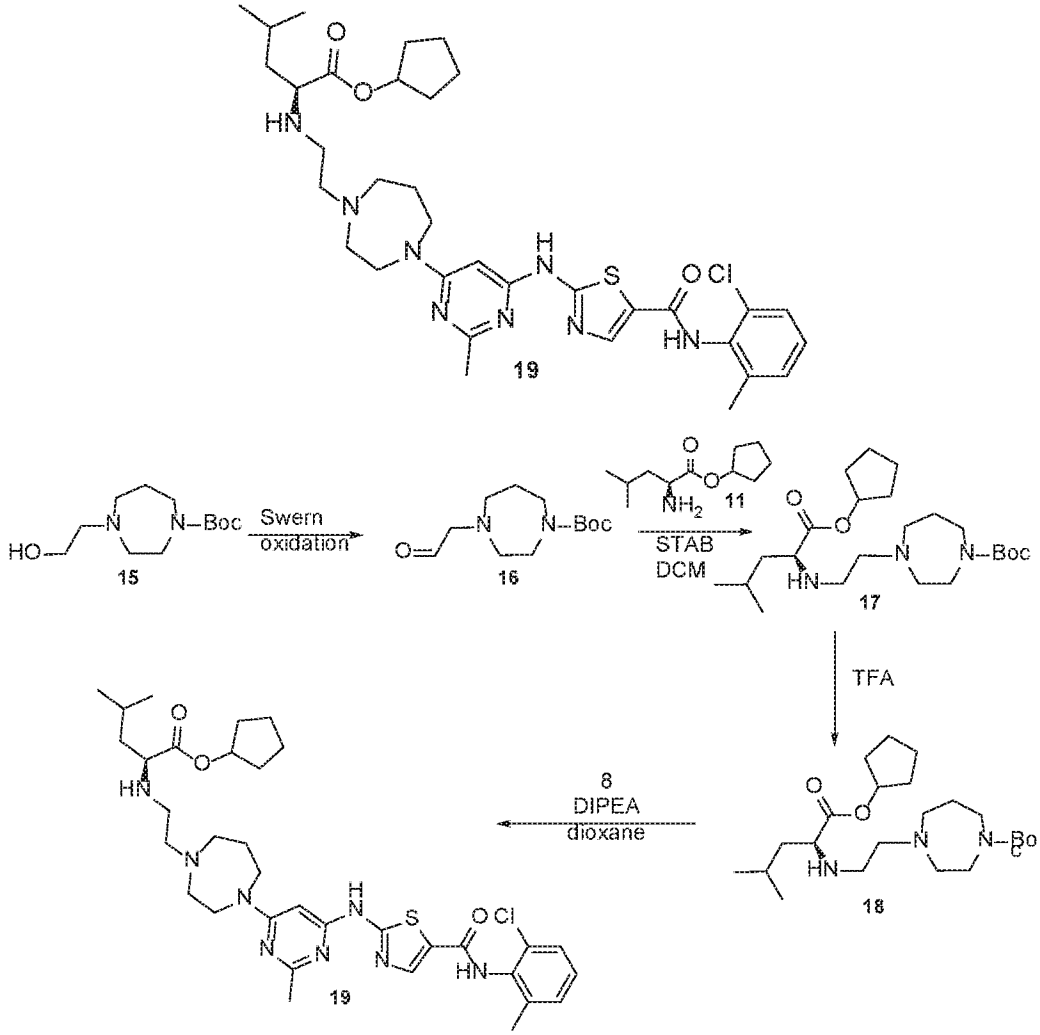


Scheme 2

[00107] Benzyloxycarbonyl (Boc) protected piperazine 9 was oxidized to give aldehyde 10. Compound 12 was obtained by treating compound 12 with compound 11 in the presence of sodium triacetoxyborohydride (STAB) in DCM.

[00108] Compound 13 can then be obtained by treating compound 12 with TFA. Subsequent coupling of compound 13 with compound 8 in the presence of DIPEA can afford compound 14.

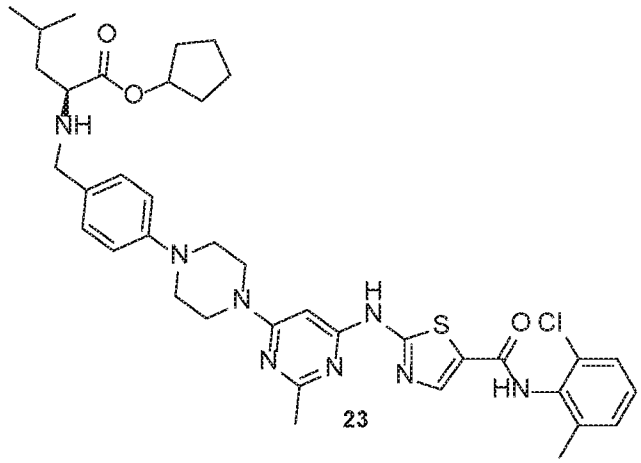
Example 3: Synthesis of compound 19

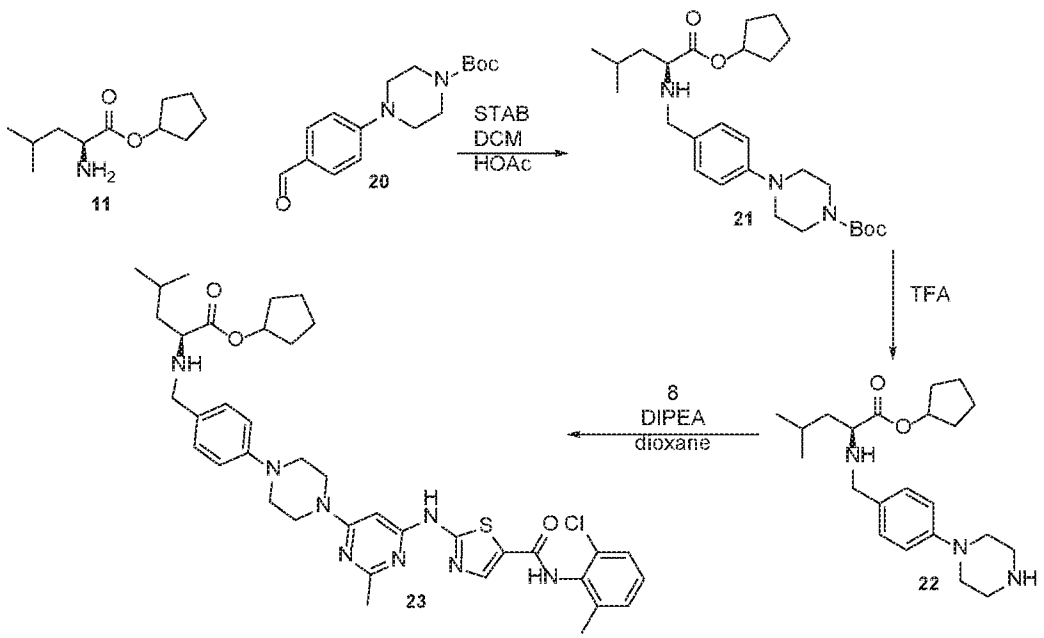


Scheme 3

[00109] The synthesis of compound 19 can be accomplished as shown in Scheme 3.

Example 4: Synthesis of compound 23

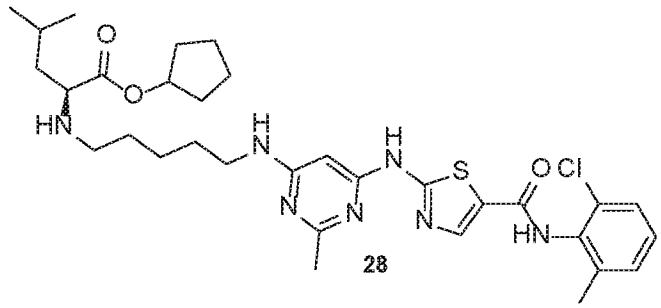


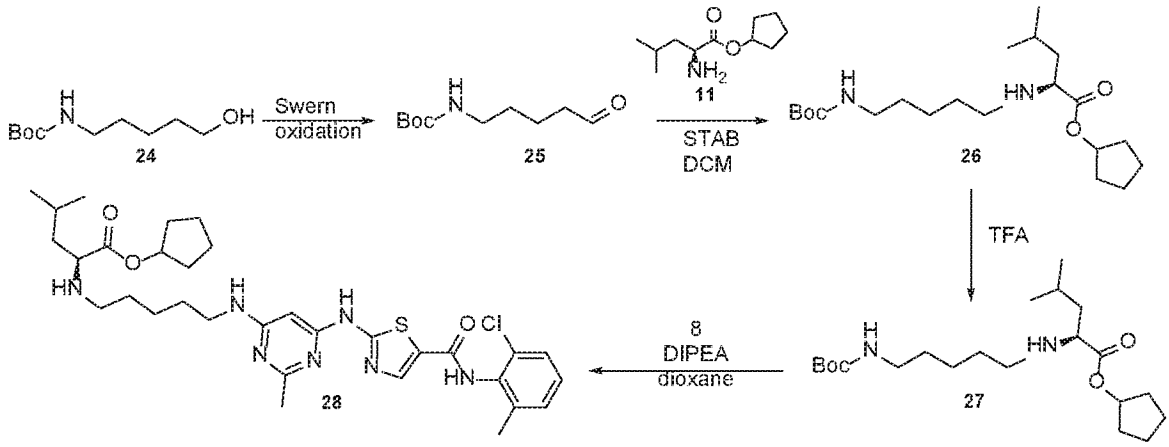


Scheme 4

[00110] Compound 23 was synthesized as show in Scheme 4.

Example 5: Synthesis of compound 28

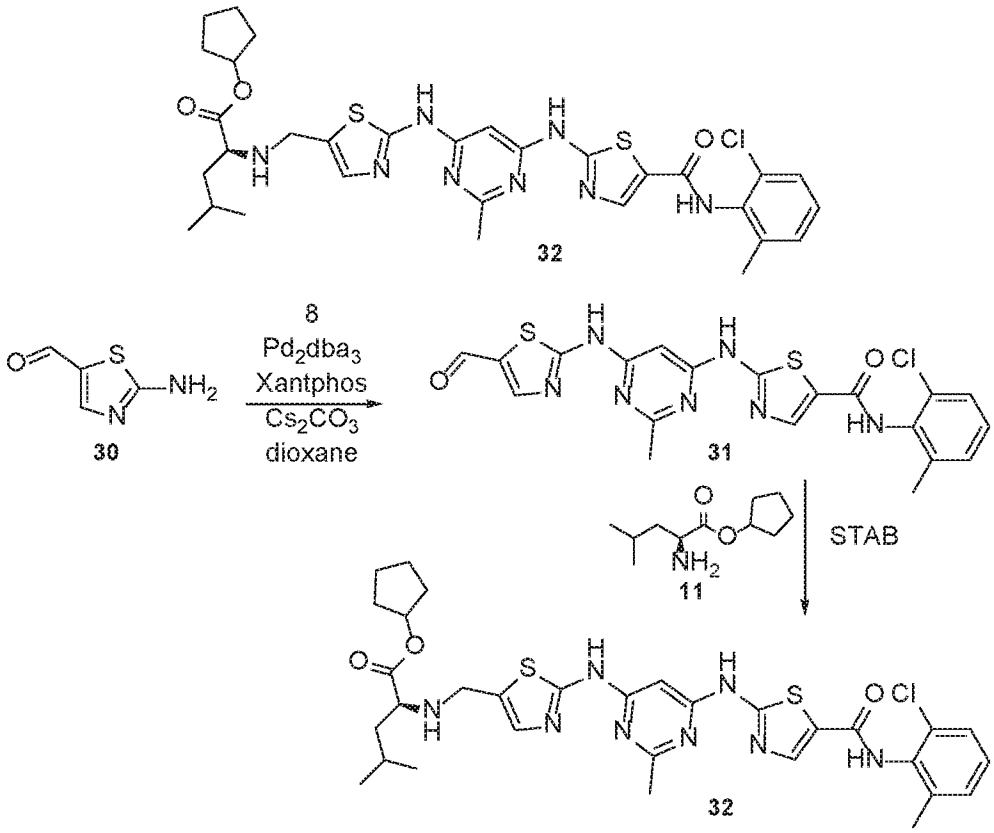




Scheme 5

[00111] Compound 28 can be synthesized as shown in Scheme 5.

Example 6: Synthesis of compound 32



Scheme 6

[00112] Compound 32 can be synthesized as shown in Scheme 6.

Example 7: Src and ERK inhibition studies in murine microglia and astrocytes

[00113] Compounds 14, 19, 23, and 28 were tested to determine whether they were inhibitors of Src and even Src-specific inhibitors in microglia. Primary murine microglia cultures were treated 24hr with increasing concentrations of compounds 14, 19, 23, and 28 (0.001, 0.01, 0.1, 1, 10 μM) or DMSO vehicle. Cells were lysed for SDS-PAGE and western blotted using anti-p-Src and p-ERK antibodies with anti-Src and ERK antibodies used to assess loading. Data are the average +/- SD of 6-8 independent experiments. See FIGS. 1 (p-Src) and 2 (p-ERK). The data not only demonstrate that compounds 14, 19, 23, and 28 are inhibitors of Src, but also that the four compounds are Src-specific inhibitors. Data (not shown) also show that compounds 14, 19, 23, and 28 are inhibitors of Src in astrocytes.

Example 8: TNFα secretion studies

[00114] Compounds 14, 19, 23, and 28 were evaluated to determine if they decrease TNFα secretion in murine microglia and astrocytes in a dose-dependent fashion. Compounds 19 and 23 were the two compounds that most dramatically decreased TNFα secretion in murine microglia and astrocytes as shown in FIG. 3, where panels (a) and (b) are microglia and astrocyte

experiments with compound 19, respectively; and FIG. 4, where panels (a) and (b) are microglia and astrocyte experiments with compound 23, respectively.

[00115] Primary murine microglia and astrocyte cultures were treated 24hr with increasing concentrations of compound 19 and 23 (0.001, 0.01, 0.1, 1, 10 μM) or DMSO vehicle (0). Media was taken for TNFa ELISA and LDH release assays. Data are representative of 3 independent experiments.

Example 9: Oral availability

[00116] Male Sprague Dawley rats were gavage with 10 mg/kg of compound 23 dissolved in 40%PEG400, 15% Cremophor, 10% DMSO in water and plasma and brains collected at 4, 8, and 12 hours post gavage for quantitation of drug. The data (not shown) show that compound 23 is orally available.

Example 10: Attenuation of cytokine levels in brain and spleen

[00117] Ten month old female APP/PS1 and littermate control C57BL/6 wild type mice were orally gavaged daily for 7 days with vehicle (a formulation cocktail: 40% PEG400, 15% Cremophor, 10% DMSO in ddH_2O) or compound 19 (10 mg/kg) or compound 23 (10 mg/kg). On day 8 temporal cortices were collected for cytokine or soluble Aβ ELISA for comparison to spleen ELISAs. Data are average values +/- SD from n=3-6 mice per group, *$p<0.05$. The data (not shown) show that compounds 19 and 23 attenuate cytokines levels in brains and spleens as well as Aβ levels in the brains of APP/PS1 mice, thus demonstrating that compounds of the various embodiments described herein can be useful in the treatment of, among other diseases, Alzheimer's disease.

[00118] The disclosure provides for the following embodiments, the numbering of which is not to be construed as designating levels of importance:

[00119] Embodiment 1 relates to a compound of the formula (I):

API—LG—ESM

(I)

wherein,

API is a monovalent substituent group of at least one of an ABL1 inhibitor, BCR-ABL inhibitor, FAK inhibitor, SRC inhibitor, LYN inhibitor SYK inhibitor, ERK inhibitor, Jun kinase (JNK) inhibitor, p38 kinase inhibitor, MEK inhibitor, IKK inhibitor, leucine-rich repeat kinase inhibitor, protein phosphatase inhibitor, and a calcineurin inhibitor;

LG is a divalent substituent group of a linking group; and

ESM is a monovalent substituent group of an esterase sensitive motif;

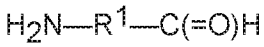
or a pharmaceutically acceptable salt thereof.

[00120] Embodiment 2 relates to the compound of Embodiment 1, wherein API is monovalent substituent group of at least one of an ABL1 inhibitor, BCR-ABL inhibitor, FAK inhibitor, SRC inhibitor, LYN inhibitor and SYK inhibitor.

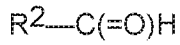
[00121] Embodiment 3 relates to the compound of Embodiments 1-2, wherein API is a SRC-selective inhibitor.

[00122] Embodiment 4 relates to the compound of Embodiments 1-3, wherein LG is a divalent substituent group formed from an amino aldehyde.

[00123] Embodiment 5 relates to the compound of Embodiments 1-4, wherein LG is a divalent substituent group formed from a compound of formula (II) or (III):



(II)



(III)

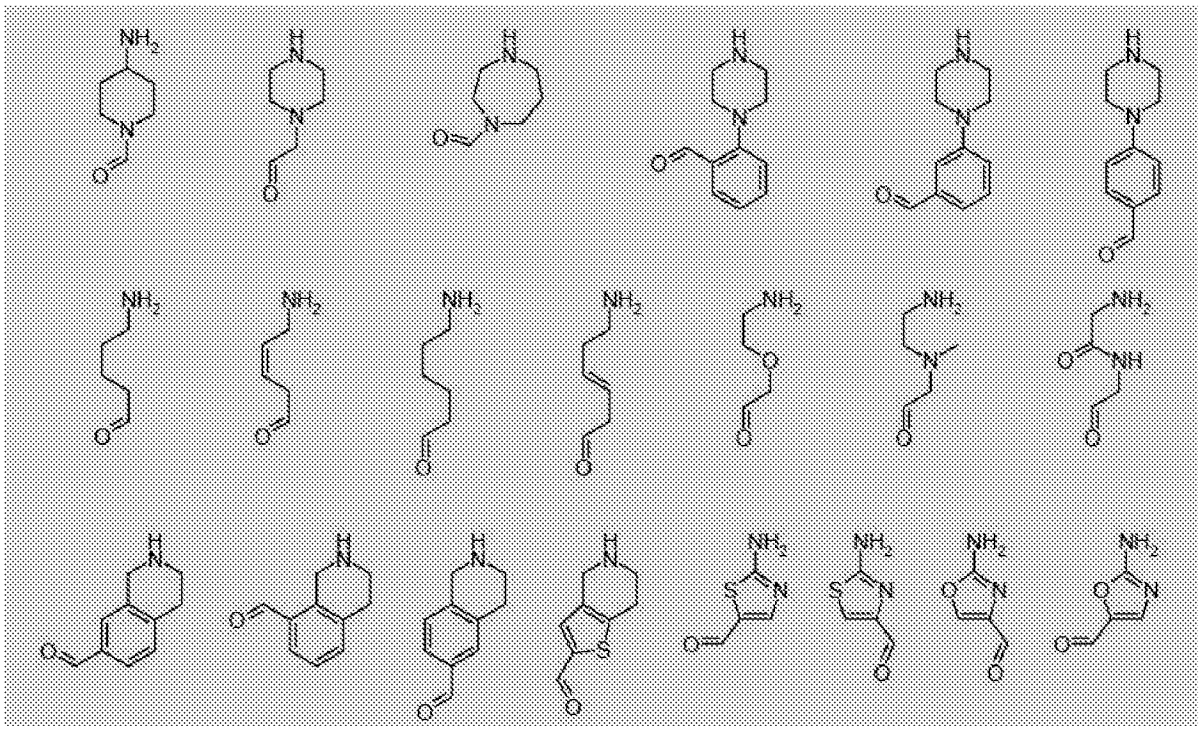
wherein,

R^1 is a divalent substituent group of a hydrocarbon;

R^2 is a monovalent substituent group of a nitrogen-containing heterocyle, a monovalent substituent group of a nitrogen-containing heteroaryl, or a monovalent substituent group of a nitrogen-containing hydrocarbon;

wherein each hydrocarbon independently is optionally substituted and optionally interrupted.

[00124] Embodiment 6 relates to the compound of Embodiments 1-5, wherein LG is a divalent substituent group formed from an amino aldehyde, illustrated below



[00125] Embodiment 7 relates to the compound of Embodiments 1-6, wherein LG is a divalent substituent group formed from an amino aldehyde, wherein the amino group, NH or NH2, and the aldehyde group, C(=O)H, is separated from one another by about 200 pm to about 1,500 pm.

[00126] Embodiment 8 relates to the compound of Embodiments 1-7, wherein LG is a divalent substituent group, such that API and ESM are separated from one another by about 300 pm to about 2,000 pm.

[00127] Embodiment 9 relates to the compound of Embodiments 1-8, wherein each of LG--ESM and LG--API independently comprise linkages, such that the functional groups that provide such linkages are selected from a combination of one of (a) and one of (b):

(a) aldehyde, isocyanate, isothiocyanate, halogen, sulfonic acid, sulfonic acid chloride, carboxylic acid, carboxylic acid chloride, hydroxyl, and protected hydroxyl;

(b) alkylhalogenide, thiol, hydroxyl, acetylene, boronic acid, and amine.

[00128] Embodiment 10 relates to the compound of Embodiments 1-9, wherein ESM is a substrate of human carboxylesterase-1.

[00129] Embodiment 11 relates to the compound of Embodiment 1-10, wherein ESM is a monovalent substituent group of at least one of α-naphthyl ester (e.g., acetate, propionate, butyrate, valerate, caproate, caprylate, caprate, laurate, myristate, palmitate, stearate, or nonanoate), naphthol AS ester (e.g.,

acetate, propionate, nonanoate, phenyl acetate, phenyl propionate, phenyl butyrate, AS-D acetate, or AS-LC acetate), and naphthol AS chloroacyl ester (e.g., AS-D chloroacetate, AS β-chloropropionate, naphthol AS Ɛ-aminocaproate HBr, indoxyl acetate, or 5-bromo-indoxyl acetate), 4-nitrophenyl acetate, 4-methylumbelliferyl acetate, naphthol AS-D chloroacetate, 5-bromo-4-chloro-3-indolyl acetate, 3,6-diacetoxyphthalonitrile, 5(6)-carboxy-2′,7′-dichlorofluorescein diacetate, 1-naphthyl propionate, 4-methylumbelliferyl butyrate, N-acetyl-DL-β-phenylalanine, DL-α-palmitin, 3-(2-benzoxazolyl)umbelliferyl acetate, 5-bromo-4-chloro-3-indolyl acetate, 8-butyryloxypyrene-1,3,6-trisulfonic acid trisodium salt, fluorescein dilaurate, indoxyl acetate, 4-methylumbelliferyl acetate, 4-methylumbelliferyl butyrate, naphthol AS-D chloroacetate, naphthol AS-D chloroacetate, 1-naphthyl acetate, 1-naphthyl butyrate, 4-nitrophenyl dodecanoate, 4-nitrophenyl myristate, 4-nitrophenyl octanoate, 8-octanoyloxypyrene-1,3,6-trisulfonic acid trisodium salt, paraoxon-ethyl, resorufin acetate, and a hydroxy-protected 5-phenyl-3-hydroxypyrrolyl L-lactate substrate.

[00130] Embodiment 12 relates to the compound of Embodiments 1-11, which is a compound of the formula (IV) or (V):

[Dasatinib] – [LG] – [cyclo-pentyl ester of L-leucine]

(IV)

or

[Bafetinib] – [LG] – [cyclo-pentyl ester of L-leucine]

(V)

wherein,

LG is a divalent substituent group of a hydrocarbon comprising at least one of alkyl, alkenyl, nitrogen-containing heterocyle, and nitrogen-containing heteroaryl; wherein each of the alkyl, alkenyl, nitrogen-containing heterocyle, and nitrogen-containing heteroaryl is independently optionally substituted and is optionally interrupted.

[00131] Embodiment 13 relates to a pharmaceutical composition comprising a compound of Embodiments 1-12, and a pharmaceutically acceptable carrier.

[00132] Embodiment 14 relates to a method of medical treatment comprising administering to an animal in need of such medical treatment, or at risk thereof, an effective amount of a compound of Embodiments 1-12 or the pharmaceutical composition of Embodiment 13, for a period of time effective to treat the animal.

[00133] Embodiment 15 relates to the method of Embodiment 14, wherein the animal is a human.

[00134] Embodiment 16 relates to the method of Embodiments 14-15, wherein the medical treatment comprises at least one of:

targeting cells of monocytic origin,

targeting microglia,

inhibiting at least one of: Lyn, Src, IKK, ERK, JNK, p38, calcineurin, and LRRK2;

selectively accumulating in microglia,

penetrating the blood-brain barrier,

treating inflammation of the peripheral nervous or organ systems,

treating rheumatoid arthritis,

treating irritable bowel syndrome (IBS),

treating inflammation in the central nervous system (CNS),

treating inflammation in the peripheral nervous system (PNS),

treating Alzheimer's disease (AD),

treating Parkinson's disease (PD),

treating cancer,

treating Crohn's disease,

treating respiratory distress syndrome,

treating glomerulonephritis, and

treating pulmonary emphysema.

[00135] Embodiment 17 relates to the method of Embodiments 14-16, wherein the administration is systemic.

[00136] Embodiment 18 relates to the method of Embodiments 14-17, wherein the administration occurs for a period of time of at least about 1 month.

[00137] Embodiment 19 relates to the method of Embodiments 14-17, wherein the administration occurs for a period of time of at least about 3 months.

[00138] Embodiment 20 relates to the method of Embodiments 14-19, wherein the administration is at least once-daily (OD).

[00139] Embodiment 21 relates to the method of Embodiment 14-19, wherein the administration is at least twice-daily (BID).

[00140] Embodiment 22 relates to the method of Embodiments 14-21, wherein the compound of Embodiments 1-12 or the pharmaceutical composition

of Embodiment 13 is co-administered to the animal with one or more additional active pharmaceutical ingredients (APIs).

[00141] Embodiment 23 relates to a compound of the formula (I), as in Embodiments 1-12, for use as a medicament for treating a patient in need of relief from at least one of inflammation of the peripheral nervous or organ systems, rheumatoid arthritis, irritable bowel syndrome (IBS), inflammation in the central nervous system (CNS), inflammation in the peripheral nervous system (PNS), Alzheimer's disease (AD), Parkinson's disease (PD), cancer, Crohn's disease, respiratory distress syndrome, glomerulonephritis, and pulmonary emphysema.

CLAIMS

What is claimed is:

1. A compound of formula (I):

API—LG—ESM

(I)

wherein,

API is a monovalent substituent group of at least one of an ABL1 inhibitor, BCR-ABL inhibitor, FAK inhibitor, SRC inhibitor, LYN inhibitor SYK inhibitor, ERK inhibitor, Jun kinase (JNK) inhibitor, p38 kinase inhibitor, MEK inhibitor, IKK inhibitor, leucine-rich repeat kinase inhibitor, protein phosphatase inhibitor, and a calcineurin inhibitor;

LG is a divalent substituent group of a linking group; and

ESM is a monovalent substituent group of an esterase sensitive motif;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein API is monovalent substituent group of at least one of an ABL1 inhibitor, BCR-ABL inhibitor, FAK inhibitor, SRC inhibitor, LYN inhibitor and SYK inhibitor.

3. The compound of claim 1, wherein API is a SRC-selective inhibitor.

4. The compound of claim 1, wherein LG is a divalent substituent group formed from an amino aldehyde.

5. The compound of claim 1, wherein LG is a divalent substituent group formed from a compound of formula (II) or (III):

$H_2N—R^1—C(=O)H$

(II)

$R^2—C(=O)H$

(III)

wherein,

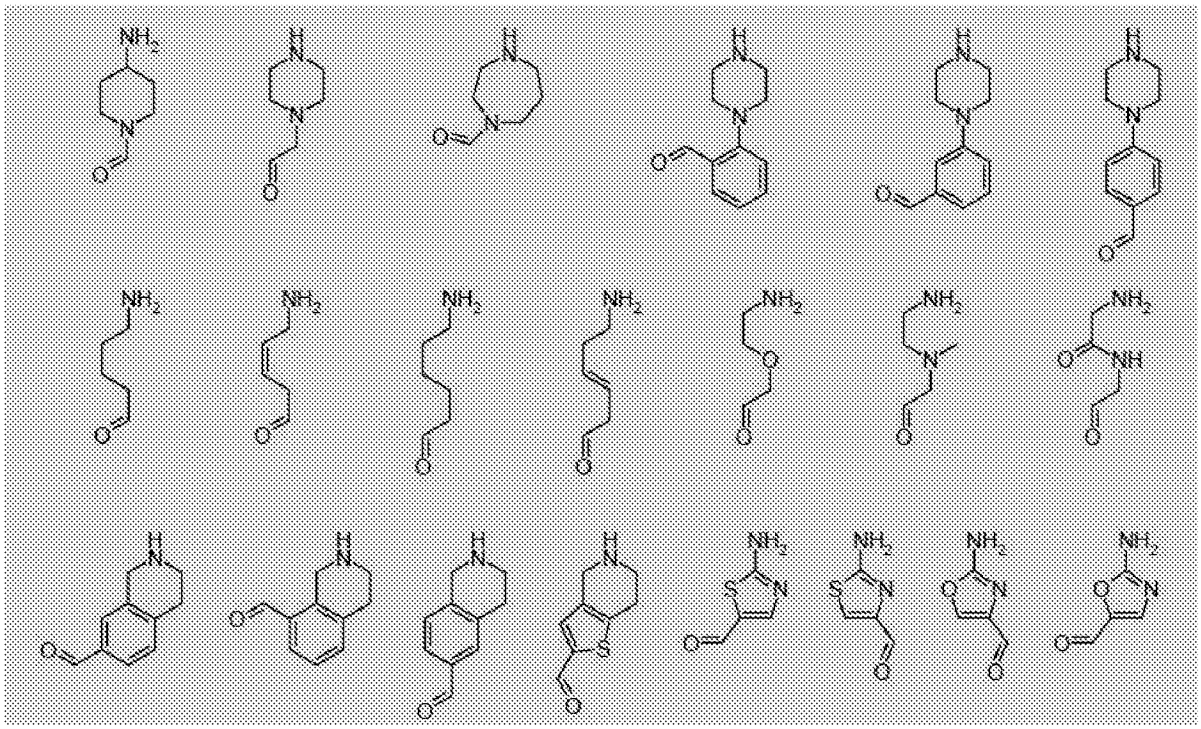
R^1 is a divalent substituent group of a hydrocarbon;

R^2 is a monovalent substituent group of a nitrogen-containing heterocyle, a monovalent substituent group of a nitrogen-containing

heteroaryl, or a monovalent substituent group of a nitrogen-containing hydrocarbon;

wherein each hydrocarbon independently is optionally substituted and optionally interrupted.

6. The compound of claim 1, wherein LG is a divalent substituent group formed from an amino aldehyde, illustrated below



7. The compound of claim 1, wherein LG is a divalent substituent group formed from an amino aldehyde, wherein the amino group, NH or NH2, and the aldehyde group, C(=O)H, is separated from one another by about 200 pm to about 1,500 pm.

8. The compound of claim 1, wherein LG is a divalent substituent group, such that API and ESM are separated from one another by about 300 pm to about 2,000 pm.

9. The compound of claim 1, wherein each of LG--ESM and LG--API independently comprise linkages, such that the functional groups that provide such linkages are selected from a combination of one of (a) and one of (b):

(a) aldehyde, isocyanate, isothiocyanate, halogen, sulfonic acid, sulfonic acid chloride, carboxylic acid, carboxylic acid chloride, hydroxyl, and protected hydroxyl;

(b) alkylhalogenide, thiol, hydroxyl, acetylene, boronic acid, and amine.

10. The compound of claim 1, wherein ESM is a substrate of human carboxylesterase-1.

11. The compound of claim 1, wherein ESM is a monovalent substituent group of at least one of α-naphthyl ester (e.g., acetate, propionate, butyrate, valerate, caproate, caprylate, caprate, laurate, myristate, palmitate, stearate, or nonanoate), naphthol AS ester (e.g., acetate, propionate, nonanoate, phenyl acetate, phenyl propionate, phenyl butyrate, AS-D acetate, or AS-LC acetate), and naphthol AS chloroacyl ester (e.g., AS-D chloroacetate, AS β-chloropropionate, naphthol AS Ɛ-aminocaproate HBr, indoxyl acetate, or 5-bromo-indoxyl acetate), 4-nitrophenyl acetate, 4-methylumbelliferyl acetate, naphthol AS-D chloroacetate, 5-bromo-4-chloro-3-indolyl acetate, 3,6-diacetoxyphthalonitrile, 5(6)-carboxy-2′,7′-dichlorofluorescein diacetate, 1-naphthyl propionate, 4-methylumbelliferyl butyrate, N-acetyl-DL-β-phenylalanine, DL-α-palmitin, 3-(2-benzoxazolyl)umbelliferyl acetate, 5-bromo-4-chloro-3-indolyl acetate, 8-butyryloxypyrene-1,3,6-trisulfonic acid trisodium salt, fluorescein dilaurate, indoxyl acetate, 4-methylumbelliferyl acetate, 4-methylumbelliferyl butyrate, naphthol AS-D chloroacetate, naphthol AS-D chloroacetate, 1-naphthyl acetate, 1-naphthyl butyrate, 4-nitrophenyl dodecanoate, 4-nitrophenyl myristate, 4-nitrophenyl octanoate, 8-octanoyloxypyrene-1,3,6-trisulfonic acid trisodium salt, paraoxon-ethyl, resorufin acetate, and a hydroxy-protected 5-phenyl-3-hydroxypyrrolyl L-lactate substrate.

12. The compound of claim 1, which is a compound of the formula (IV) or (V):

[Dasatinib] – [LG] – [cyclo-pentyl ester of L-leucine]

(IV)

or

[Bafetinib] – [LG] – [cyclo-pentyl ester of L-leucine]

(V)

wherein,

LG is a divalent substituent group of a hydrocarbon comprising at least one of alkyl, alkenyl, nitrogen-containing heterocyle, and nitrogen-containing heteroaryl; wherein each of the alkyl, alkenyl, nitrogen-containing heterocyle, and nitrogen-containing heteroaryl is independently optionally substituted and is optionally interrupted.

13. A pharmaceutical composition comprising a compound of claim 1, and a pharmaceutically acceptable carrier.

14. A method of medical treatment comprising administering to an animal in need of such medical treatment, or at risk thereof, an effective amount of a compound of claim 1, for a period of time effective to treat the animal.

15. The method of claim 14, wherein the animal is a human.

16. The method of claim 14, wherein the medical treatment comprises at least one of:

targeting cells of monocytic origin,

targeting microglia,

inhibiting at least one of: Lyn, Src, IKK, ERK, JNK, p38, calcineurin, and LRRK2;

selectively accumulating in microglia,

penetrating the blood-brain barrier,

treating inflammation of the peripheral nervous or organ systems,

treating rheumatoid arthritis,

treating irritable bowel syndrome (IBS),

treating inflammation in the central nervous system (CNS),

treating inflammation in the peripheral nervous system (PNS),

treating Alzheimer's disease (AD),

treating Parkinson's disease (PD),

treating cancer,

treating Crohn's disease,

treating respiratory distress syndrome,

treating glomerulonephritis, and

treating pulmonary emphysema.

17. The method of claim 14, wherein the administration is systemic.

18. The method of claim 14, wherein the administration occurs for a period of time of at least about 1 month.

19. The method of claim 14, wherein the administration occurs for a period of time of at least about 3 months.

20. The method of claim 14, wherein the administration is at least once-daily (OD).

21. The method of claim 14, wherein the administration is at least twice-daily (BID).

22. The method of claim 14, wherein the compound of claim 1 is co-administered to the animal with one or more additional active pharmaceutical ingredients (APIs).

23. A compound of the formula (I), as in claim 1, for use as a medicament for treating a patient in need of relief from at least one of inflammation of the peripheral nervous or organ systems, rheumatoid arthritis, irritable bowel syndrome (IBS), inflammation in the central nervous system (CNS), inflammation in the peripheral nervous system (PNS), Alzheimer's disease (AD), Parkinson's disease (PD), cancer, Crohn's disease, respiratory distress syndrome, glomerulonephritis, and pulmonary emphysema.

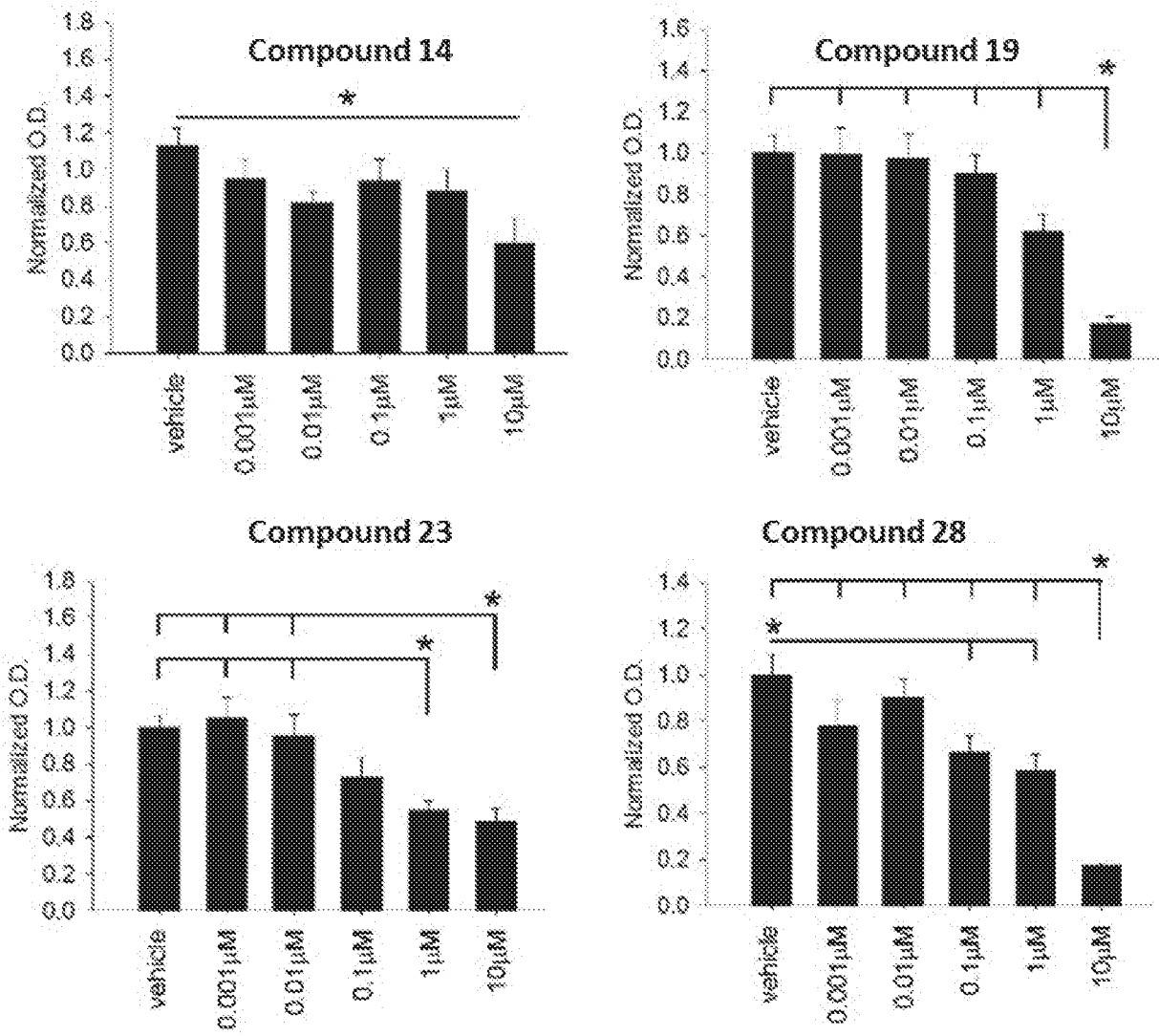

Compound 14
Normalized O.D.
vehicle
0.001μM
0.01μM
0.1μM
1μM
10μM
Compound 19
Normalized O.D.
vehicle
0.001μM
0.01μM
0.1μM
1μM
10μM
Compound 23
Normalized O.D.
vehicle
0.001μM
0.01μM
0.1μM
1μM
10μM
Compound 28
Normalized O.D.
vehicle
0.001μM
0.01μM
0.1μM
1μM
10μM

FIG. 1

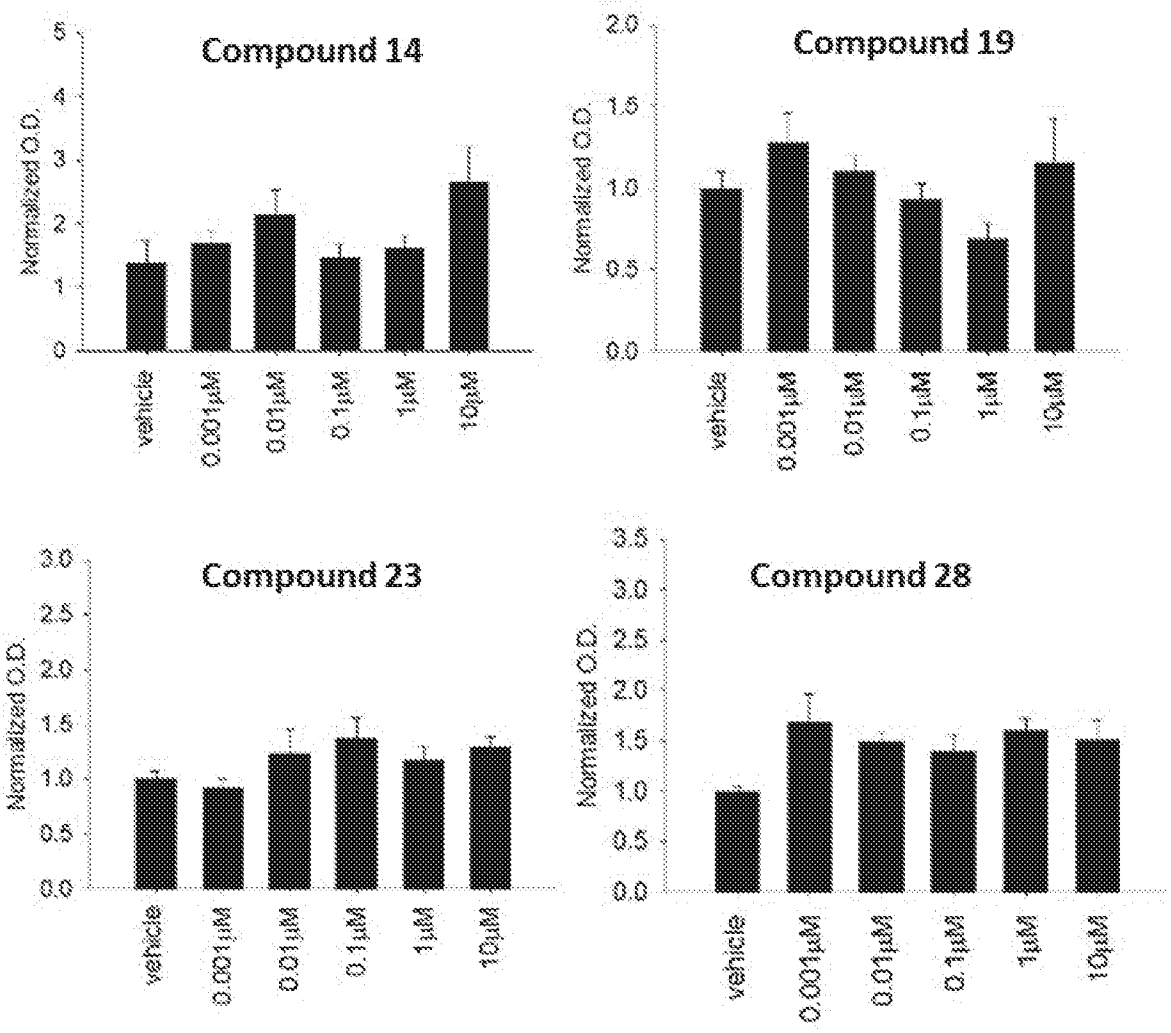

Compound 14
Normalized O.D.
0
1
2
3
4
5
vehicle
0.001μM
0.01μM
0.1μM
1μM
10μM
Compound 19
Normalized O.D.
0.0
0.5
1.0
1.5
2.0
vehicle
0.001μM
0.01μM
0.1μM
1μM
10μM
Compound 23
Normalized O.D.
0.0
0.5
1.0
1.5
2.0
2.5
3.0
vehicle
0.001μM
0.01μM
0.1μM
1μM
10μM
Compound 28
Normalized O.D.
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
vehicle
0.001μM
0.01μM
0.1μM
1μM
10μM

FIG. 2

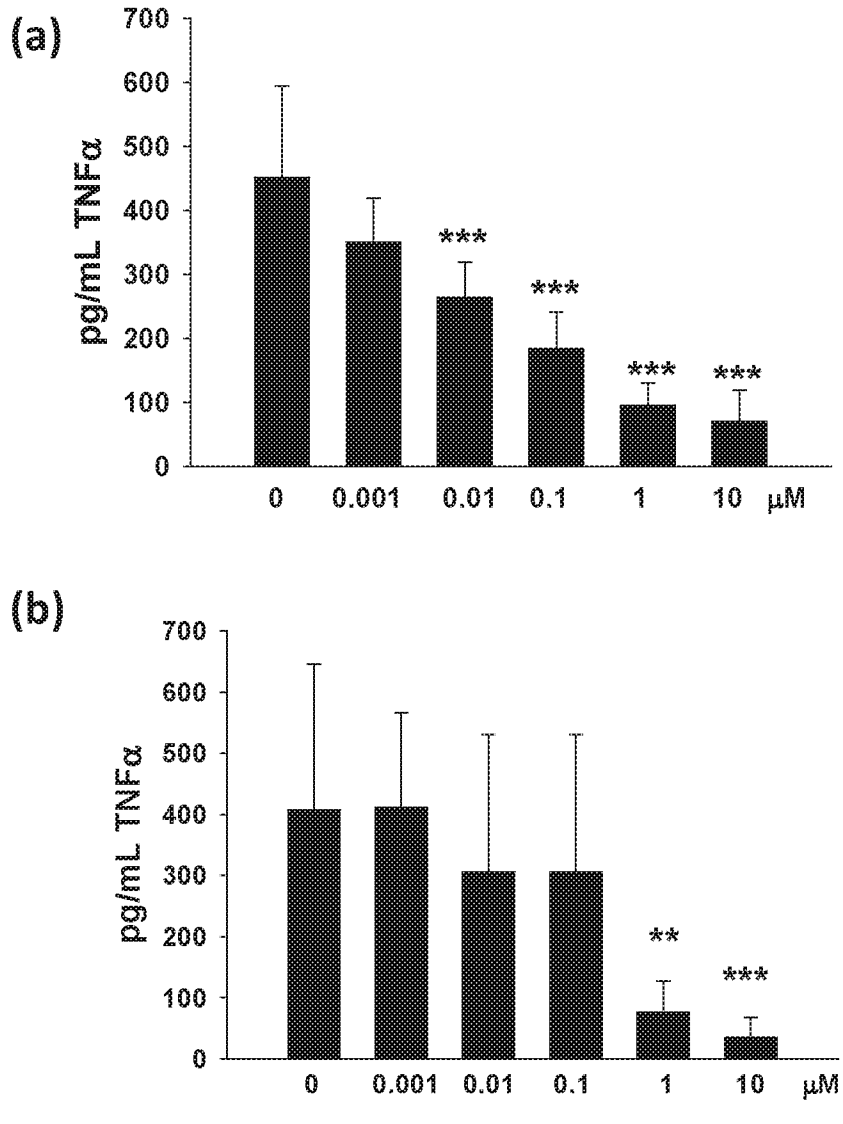

(a)
pg/mL TNFα
700
600
500
400
300
200
100
0
***
***
***
***
0
0.001
0.01
0.1
1
10
μM
(b)
pg/mL TNFα
700
600
500
400
300
200
100
0
**
***
0
0.001
0.01
0.1
1
10
μM

FIG. 3

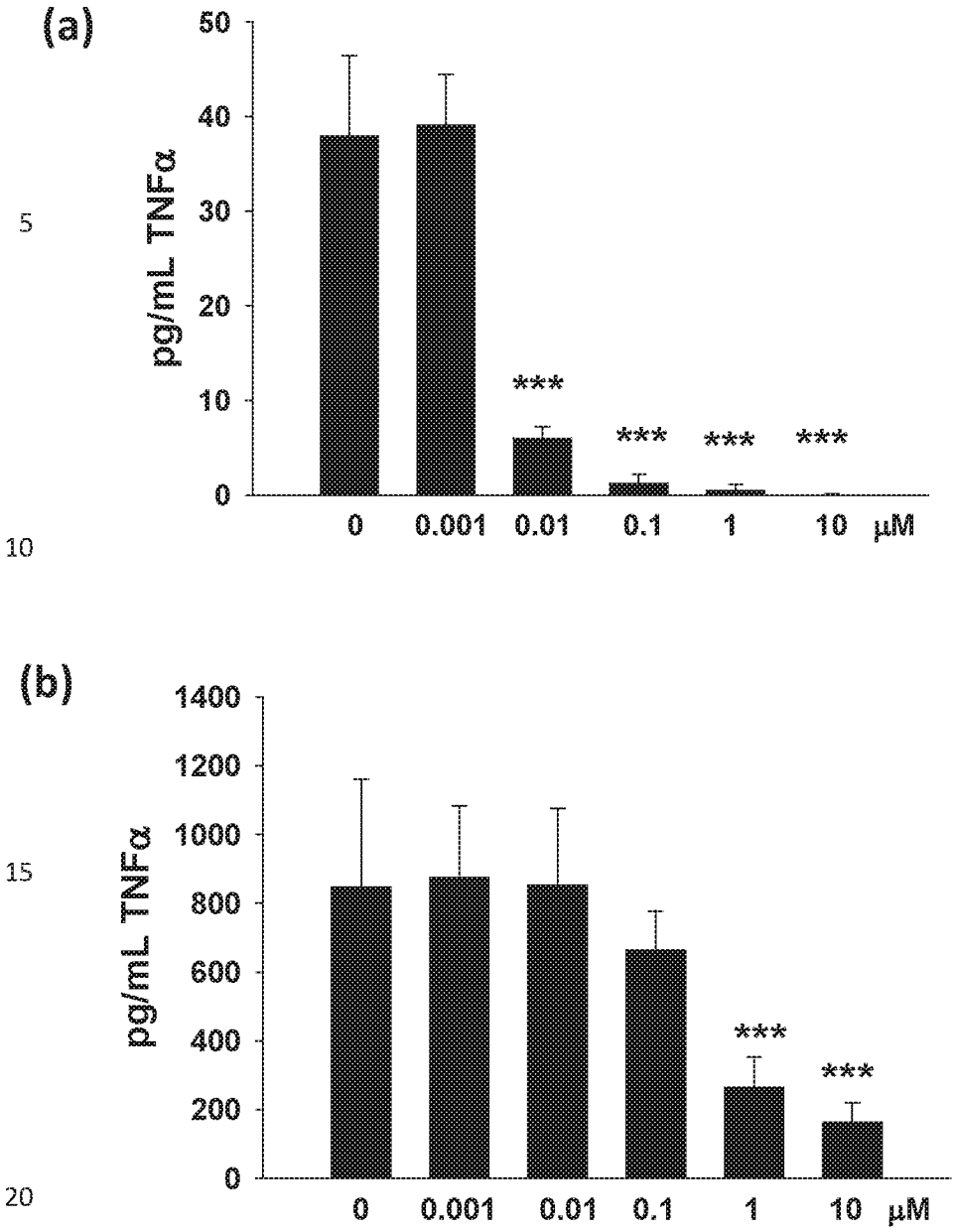

(a)
pg/mL TNFα
50
40
30
20
10
0
***
***
***
***
0
0.001
0.01
0.1
1
10
μM
(b)
pg/mL TNFα
1400
1200
1000
800
600
400
200
0
***
***
0
0.001
0.01
0.1
1
10
μM

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/066011

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 47/00; A61K 47/46; A61K 47/48; C07D 417/02; C07D 417/04; C07D 417/14 (2017.01)
CPC - A61K 47/00; A61K 47/46; A61K 47/48; C07D 417/02; C07D 417/04; C07D 417/14 (2017.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2005/0256069 A1 (MANOHARAN et al) 17 November 2005 (17.11.2005) entire document	1-3, 8, 10, 12-23
A	US 2014/0080839 A1 (NEKTAR THERAPEUTICS) 20 March 2014 (20.03.2014) entire document	1-3, 8, 10, 12-23
A	US 2014/0329828 A1 (NEKTAR THERAPEUTICS) 06 November 2014 (06.11.2014) entire document	1-3, 8, 10, 12-23
A	WO 2014/182950 A1 (NIMBUS APOLLO INC) 13 November 2014 (13.11.2014) entire document	1-3, 8, 10, 12-23

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"I." document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 April 2017	08 MAY 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/066011

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet

Claims 1-3, 8, 10, and 12-23 have been analyzed subject to the restriction that the claims read on a compound of formula (I): wherein API is a monovalent substituent group; LG is a divalent substituent group of a linking group; ESM is a monovalent substituent group of an esterase sensitive motif, wherein the compound of formula (I) is a compound of formula (IV), wherein LG is a divalent substituent group of a hydrocarbon comprising alkyl, which is unsubstituted.

Claims 1-3, 8, 10, and 12-23 have been analyzed subject to the restriction that the claims read on the formula (I) as described in the Response to the Invitation to Pay Additional Fees in the International Application dated 28 February 2017 as further restricted to the variable definitions listed below. The claims are restricted to a compound of formula (I): wherein API is a monovalent substituent group; LG is a divalent substituent group of a linking group; ESM is a monovalent substituent group of an esterase sensitive motif, wherein the compound of formula (I) is a compound of formula (V), wherein LG is a divalent substituent group of a hydrocarbon comprising alkyl, which is unsubstituted.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

1-3, 8, 10, 12-23

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-23 are drawn to compounds of formula (I) or a pharmaceutically acceptable salt thereof, pharmaceutical compositions thereof, methods thereof, and compounds for use as a medicament.

The first invention of Group I+ is restricted to a compound of formula (I): wherein API is a monovalent substituent group; LG is a divalent substituent group of a linking group; ESM is a monovalent substituent group of an esterase sensitive motif, wherein the compound of formula (I) is a compound of formula (IV), wherein LG is a divalent substituent group of a hydrocarbon comprising alkyl, which is unsubstituted; pharmaceutical compositions thereof; methods thereof; and compounds for use as a medicament. It is believed that claims 1-3, 8, 10, and 12-23 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of formula (I): wherein API is a monovalent substituent group; LG is a divalent substituent group of a linking group; ESM is a monovalent substituent group of an esterase sensitive motif, wherein the compound of formula (I) is a compound of formula (V), wherein LG is a divalent substituent group of a hydrocarbon comprising alkyl, which is unsubstituted; pharmaceutical compositions thereof; methods thereof; and compounds for use as a medicament. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables API, LG, and ESM.

The Groups I+ share the technical features of a compound having the core structure of formula (I); a pharmaceutical composition comprising a compound, and a pharmaceutically acceptable carrier; a method of medical treatment comprising administering to an animal in need of such medical treatment, or at risk thereof, an effective amount of a compound for a period of time effective to treat the animal; and a compound having the core structure of the formula (I), for use as a medicament for treating a patient in need of relief from at least one of inflammation of the peripheral nervous or organ systems, rheumatoid arthritis, irritable bowel syndrome (IBS), inflammation in the central nervous system (CNS), inflammation in the peripheral nervous system (PNS), Alzheimer's disease (AD), Parkinson's disease (PD), cancer, Crohn's disease, respiratory distress syndrome, glomerulonephritis, and pulmonary emphysema. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2005/0256069 A1 to Manoharan et al. teach a compound having the core structure of formula (I) (Para. [0800], Compound 704;...see shown structure...; Claims 1, 3 and 5); a pharmaceutical composition (Claim 1) comprising a compound, and a pharmaceutically acceptable carrier (Claim 1; Paras. [0194] and [0195]); a method of medical treatment (Claim 99; Para. [0769]) comprising administering to an animal in need of such medical treatment, or at risk thereof, an effective amount of a compound for a period of time effective to treat the animal (Claim 99; Para. [0769]); a compound having the core structure of the formula (I) (Para. [0800], Compound 704;...see shown structure...; Claims 1, 3 and 5), for use as a medicament for treating a patient in need of relief from at least one of rheumatoid arthritis (Paras. [0365] and [0747]).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.