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THIADIAZOLEOXIDES AS CXC- AND CC-
CHEMOKINE RECEPTOR LIGANDS**

(75) Inventors: **Arthur G. Taveras**, Denville, NJ (US);
Jianhua Chao, Pompton Lakes, NJ
(US); **Purakkattil J. Bijju**, Scotch
Plains, NJ (US); **Younong Yu**, Scotch
Plains, NJ (US); **Jay S. Fine**,
Bloomfield, NJ (US); **William Hipkin**,
Cranford, NJ (US); **Cynthia J. Aki**,
Livingston, NJ (US); **J. Robert
Merritt**, Ewing, NJ (US); **Ge Li**,
Shanghai (CN); **John J. Baldwin**,
Gwynedd Valley, PA (US); **Gaifa Lai**,
Edison, NJ (US); **Minglang Wu**,
Monmouth Junction, NJ (US); **Evan A.
Hecker**, Austin, TX (US)

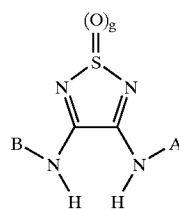
Correspondence Address:
SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
2000 GALLOPING HILL ROAD
KENILWORTH, NJ 07033-0530 (US)

(73) Assignee: **Schering Corporation Pharmacopeia,
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548/134

(57) **ABSTRACT**

Disclosed are novel compounds of the formula:



and the pharmaceutically acceptable salts and solvates thereof. Examples of groups comprising Substituent A include heteroaryl, aryl, heterocycloalkyl, cycloalkyl, aryl, alkynyl, alkenyl, aminoalkyl, alkyl or amino. Examples of groups comprising Substituent B include aryl and heteroaryl. Also disclosed is a method of treating a chemokine mediated diseases, such as, cancer, angiogenesis, angiogenic ocular diseases, pulmonary diseases, multiple sclerosis, rheumatoid arthritis, osteoarthritis, stroke and cardiac reperfusion injury, acute pain, acute and chronic inflammatory pain, and neuropathic pain using a compound of formula IA.

THIADIAZOLEDIOXIDES AND THIADIAZOLEOXIDES AS CXC- AND CC- CHEMOKINE RECEPTOR LIGANDS

REFERENCE TO RELATED APPLICATION

[0001] This Application claims the benefit of U.S. Provisional Application Serial No. 60/417,371 filed October 9, 2002.

FIELD OF THE INVENTION

[0002] The present invention relates to novel substituted thiadiazoledioxide and thiadiazolemonooxide compounds, pharmaceutical compositions containing the compounds, and the use of the compounds and formulations in treating CXC and CC-chemokine-mediated diseases.

BACKGROUND OF THE INVENTION

[0003] Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T-cells, eosinophils, basophils, neutrophils and endothelial cells to sites of inflammation and tumor growth. There are two main classes of chemokines, the CXC-chemokines and the CC-chemokines. The class depends on whether the first two cysteines are separated by a single amino acid (CXC-chemokines) or are adjacent (CC-chemokines). The CXC-chemokines include, but are not limited to, interleukin-8 (IL-8), neutrophil-activating protein-1 (NAP-1), neutrophil-activating protein-2 (NAP-2), GRO α , GRO β , GRO γ , ENA-78, GCP-2, IP-10, MIG and PF4. CC chemokines include, but are not limited to, RANTES, MIP-1 α , MIP-2 β , monocyte chemotactic protein-1 (MCP-1), MCP-2, MCP-3, CCL19, CCL21 and eotaxin. Individual members of the chemokine families are known to be bound by at least one chemokine receptor, with CXC-chemokines generally bound by members of the CXCR class of receptors, and CC-chemokines by members of the CCR class of receptors. For example, IL-8 is bound by the CXCR-1 and CXCR-2 receptors.

[0004] Since CXC-chemokines promote the accumulation and activation of neutrophils, these chemokines have been implicated in a wide range of acute and chronic inflammatory disorders including psoriasis and rheumatoid arthritis. Baggiolini et al., FEBS Lett. 307, 97 (1992); Miller et al., Crit. Rev. Immunol. 12, 17 (1992); Oppenheim et al., Annu. Rev. Immunol. 9, 617 (1991); Seitz et al., J. Clin. Invest. 87, 463 (1991); Miller et al., Am. Rev. Respir. Dis. 146, 427 (1992); Donnelly et al., Lancet 341, 643(1993).

[0005] ELRCXC chemokines including IL-8, GRO α , GRO β , GRO γ , NAP-2, and ENA-78 (Strieter et al. 1995 JBC 270 p. 27348-57) have also been implicated in the induction of tumor angiogenesis (new blood vessel growth). All of these chemokines are believed to exert their actions by binding to the 7 transmembrane G-protein coupled receptor CXCR2 (also known as IL-8RB), while IL-8 also binds CXCR1 (also known as IL-8RA). Thus, their angiogenic activity is due to their binding to and activation of CXCR2, and possible CXCR1 for IL-8, expressed on the surface of vascular endothelial cells (ECs) in surrounding vessels.

[0006] Many different types of tumors have been shown to produce ELRCXC chemokines and their production has been correlated with a more aggressive phenotype (Inoue et

al. 2000 Clin Cancer Res 6 p. 2104-2119) and poor prognosis (Yoneda et. al. 1998 J Nat Cancer Inst 90 p. 447-454). Chemokines are potent chemotactic factors and the ELRCXC chemokines have been shown to induce EC chemotaxis. Thus, these chemokines probably induce chemotaxis of endothelial cells toward their site of production in the tumor. This may be a critical step in the induction of angiogenesis by the tumor. Inhibitors of CXCR2 or dual inhibitors of CXCR2 and CXCR1 will inhibit the angiogenic activity of the ELRCXC chemokines and therefore block the growth of the tumor. This anti-tumor activity has been demonstrated for antibodies to IL-8 (Arenberg et al. 1996 J Clin Invest 97 p. 2792-2802), ENA-78 (Arenberg et al. 1998 J Clin Invest 102 p.465-72), and GRO α (Haghnegahdar et al. J. Leukoc Biology 2000 67 p. 53-62).

[0007] Many tumor cells have also been shown to express CXCR2 and thus tumor cells may also stimulate their own growth when they secrete ELRCXC chemokines. Thus, along with decreasing angiogenesis, inhibitors of CXCR2 may directly inhibit the growth of tumor cells.

[0008] Hence, the CXC-chemokine receptors represent promising targets for the development of novel anti-inflammatory and anti-tumor agents.

[0009] There remains a need for compounds that are capable of modulating activity at CXC-chemokine receptors. For example, conditions associated with an increase in IL-8 production (which is responsible for chemotaxis of neutrophil and T-cell subsets into the inflammatory site and growth of tumors) would benefit by compounds that are inhibitors of IL-8 receptor binding.

SUMMARY OF THE INVENTION

[0014] This invention also provides a method of treating a CCR7 mediated disease in a patient in need of such treatment comprising administering to said patient an effective amount of at least one compound (usually 1) of formula IA, or a pharmaceutically acceptable salt or solvate thereof.

[0015] This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt or solvate thereof.

[0016] This invention also provides a method of treating Kaposi's sarcoma, melanoma, gastric carcinoma, and non-small cell carcinoma in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt or solvate thereof.

[0017] This invention also provides a method of treating melanoma, gastric carcinoma, and non-small cell carcinoma in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt or solvate thereof.

[0018] This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt or solvate thereof, in combination with at least one anticancer agent selected from the group consisting of: (a) microtubule affecting agents, (b) antineoplastic agents, (c) anti-angiogenesis agents, or (d) VEGF receptor kinase inhibitors, (e) antibodies against the VEGF receptor, (f) interferon, and g) radiation. The compound of formula IA can be administered concurrently or sequentially with the anticancer agent.

[0019] This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt or solvate thereof, in combination with at least one (usually 1) antineoplastic agent selected from the group consisting of: gemcitabine, paclitaxel (Taxol®), 5-Fluorouracil (5-FU), cyclophosphamide (Cytosan®), temozolomide, and Vincristine.

[0020] This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt or solvate thereof, concurrently or sequentially with microtubule affecting agent, e.g., paclitaxel.

[0021] This invention also provides a method treating cancer in a patient in need of such treatment comprising administering to said patient a therapeutically effective amount of: (a) at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt or solvate thereof, concurrently or sequentially with (b) at least one (usually 1) agent selected from the group consisting of: (1) antineoplastic agents, (2) microtubule affecting agents, and (3) anti-angiogenesis agents.

[0022] This invention also provides a method of inhibiting angiogenesis in a patient in need of such treatment com-

prising administering to said patient an effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt or solvate thereof.

[0023] This invention also provides a method of treating angiogenic ocular disease (e.g., ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization) in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (usually 1) compound of formula IA, or a pharmaceutically acceptable salt or solvate thereof.

[0024] This invention also provides a method of treating a chemokine mediated (e.g., CXCR1 and/or CXCR2, or CCR7) disease or condition selected from the group consisting of: acute pain, acute inflammation, chronic inflammation, rheumatoid arthritis, acute inflammatory pain, chronic inflammatory pain, neuropathic pain, psoriasis, atopic dermatitis, asthma, COPD, adult respiratory disease, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, cardiac reperfusion injury, renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft vs. host reaction (i.e., graft vs. host disease), allograft rejections (e.g., acute allograft rejection, and chronic allograft rejection), malaria, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral ischemia, cardiac ischemia, osteoarthritis, multiple sclerosis, retinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma associated virus (i.e., Kaposi's sarcoma), meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute pancreatitis, chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred, corneal neovascularization, polymyositis, vasculitis, acne, gastric ulcers, duodenal ulcers, celiac disease, esophagitis, glossitis, air-flow obstruction, airway hyperresponsiveness (i.e., airway hyperreactivity), bronchiectasis, bronchiolitis, bronchiolitis obliterans (i.e., bronchiolitis obliterans syndrome), chronic bronchitis, cor pulmonae, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy (i.e., the treatment of burns), periodontitis, cancer, transplant reperfusion injury, early transplantation rejection (e.g., acute allograft rejection), airway hyperreactivity, allergic contact dermatitis, allergic rhinitis, alopecia areata, antiphospholipid syndromes, apl

bond, and 2 to 15 carbon atoms, preferably 2 to 12 carbon atoms, and more preferably 2 to 4 carbon atoms. Non-limiting examples of alkynyl groups include ethynyl, propynyl, 2-butylnyl, 3-methylbutynyl, n-pentylnyl, and decynyl.

[0072] "Aryl" means an aromatic monocyclic or multicyclic ring system, wherein at least one ring is aromatic, comprising about 6 to about 14 carbon atoms, and preferably about 6 to about 10 carbon atoms. Non-limiting examples of suitable aryl groups include: phenyl, naphthyl, indenyl, tetrahydronaphthyl, indanyl, anthracenyl, and fluorenyl.

[0073] "Arylalkyl" means an aryl group, as defined above, bound to an alkyl group, as defined above, wherein the alkyl group is bound to the parent moiety. Non-limiting examples of suitable arylalkyl groups include benzyl, phenethyl and naphthlenylmethyl.

[0074] "Bn" represents benzyl.

[0075] "Cycloalkyl" means saturated carbocyclic rings having 3 to 10 (e.g., 3 to 7) carbon atoms, preferably 5 to 10 carbon atoms, and more preferably 5 to 7 carbon atoms, and having one to three rings. Non-limiting examples of cycloalkyl groups include: cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and adamantyl.

[0076] "Cycloalkylalkyl" means a cycloalkyl group bound to the parent moiety through an alkyl group. Non-limiting examples include: cyclopropylmethyl and cyclohexylmethyl.

[0077] "Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising 3 to 10 carbon atoms, and preferably 5 to 10 carbon atoms, and having at least one carbon-carbon double bond. Preferred cycloalkenyl rings have 5 to 7 carbon atoms. Non-limiting examples of cycloalkyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, and norbornenyl.

[0078] "Et" represents ethyl.

[0079] "Halo" means fluoro, chloro, bromo, or iodo groups. Preferred are fluoro, chloro or bromo, and more preferred are fluoro and chloro.

[0080] "Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine or bromine, and more preferred are fluorine and chlorine.

[0081] "Haloalkyl" means an alkyl group as defined above wherein one or more hydrogen atoms on the alkyl is replaced by a halo group defined above.

[0082] "Heterocyclyl" or "heterocyclic" or "heterocycloalkyl" means a non-aromatic saturated monocyclic or multicyclic ring system (i.e., a saturated carbocyclic ring or ring system) comprising 3 to 10 ring atoms (e.g., 3 to 7 ring atoms), preferably 5 to 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls have 5 to 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom, respectively, is present as a ring atom. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of monocyclic het-

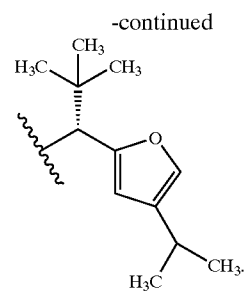
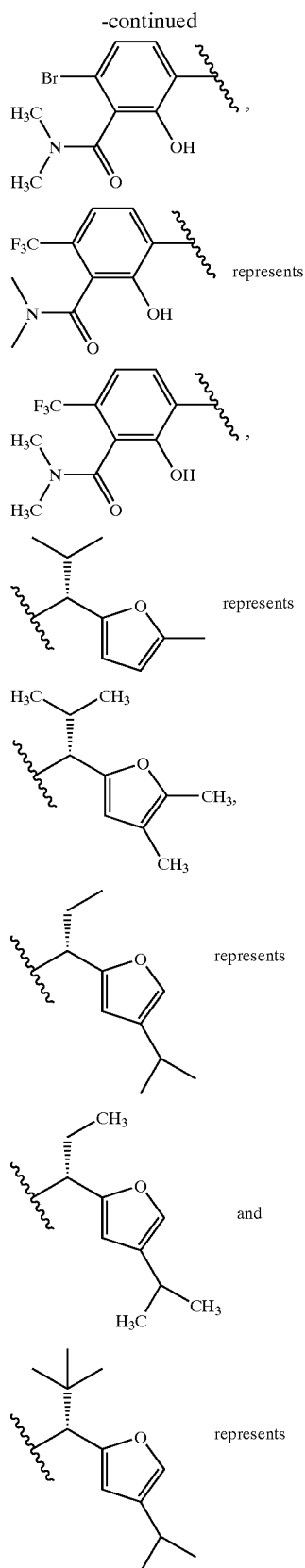
erocyclyl rings include: piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, and tetrahydrothiopyranyl.

[0083] The term heterocyclic acidic functional group is intended to include groups such as, pyrrole, imidazole, triazole, tetrazole, and the like.

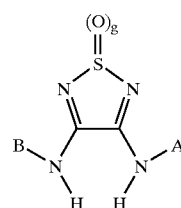
[0084] "Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising 5 to 14 ring atoms, preferably 5 to 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain 5 to 6 ring atoms. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of heteroaryls include: pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalyl, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolyl, imidazolyl, thienopyridyl, quinoxalyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolyl, benzoazaindolyl, 1,2,4-triazinyl, and benzothiazolyl.

[0085] "Heteroarylalkyl" means a heteroaryl group, as defined above, bound to an alkyl group, as defined above, where the bond to the parent moiety is through the alkyl group.

[0086] N-oxides can form on a tertiary nitrogen present in an R substituent, or on $=N-$ in a heter



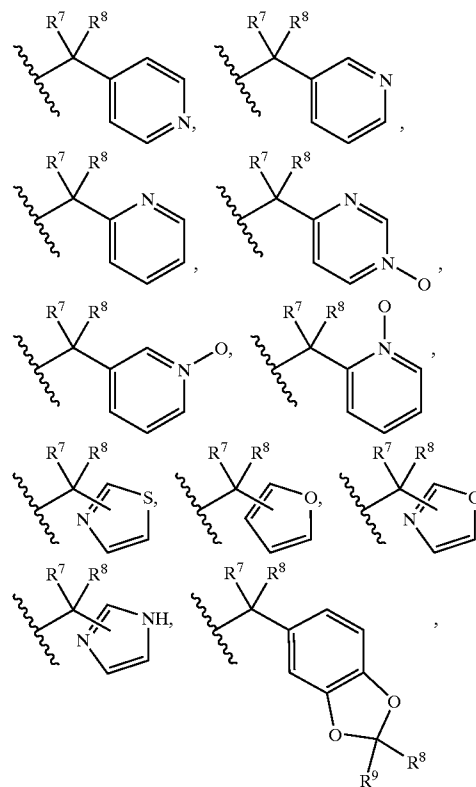
[0088] The compounds of this invention are represented by formula IA:

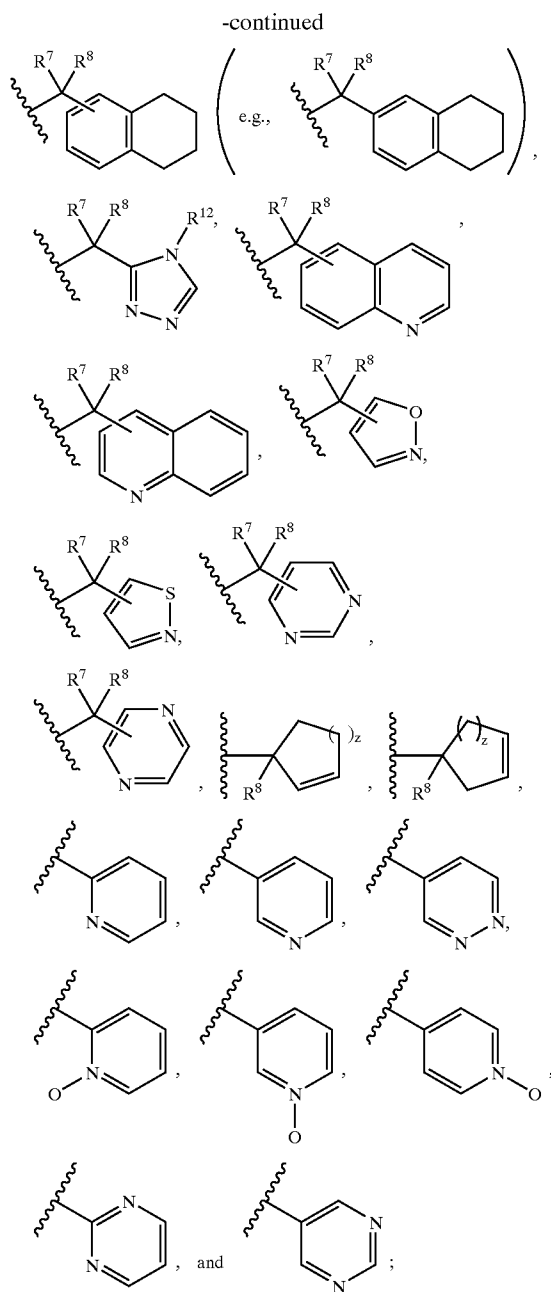
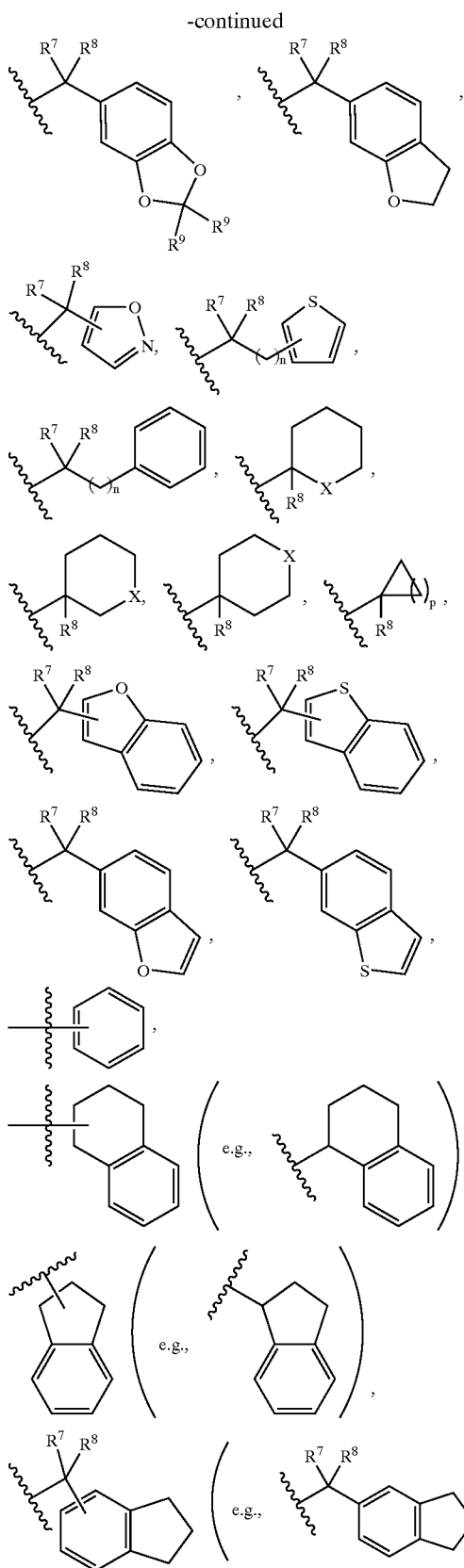


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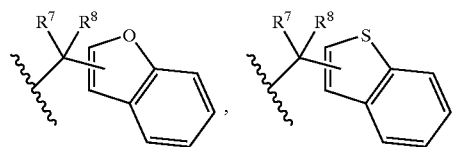
[0089] and the pharmaceutically acceptable salts (e.g., sodium or calcium salt) and solvates thereof, wherein:

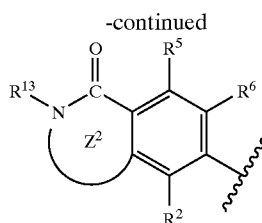
[0090] A is selected from the group consisting of:



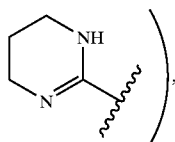


[0091] wherein the above rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R⁹ groups;

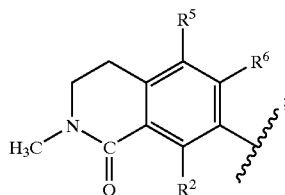




[0104] (preferably Z^1) wherein Z^1 or Z^2 is an unsubstituted or substituted saturated heterocyclic ring (preferably a 4 to 7 membered heterocyclic ring), said ring Z^1 or Z^2 optionally containing one additional heteroatom selected from the group consisting of: O, S and NR^{18} , wherein there are 1 to 3 substituents on said ring Z^1 or Z^2 , and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_2NR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$, $-NHC(O)OR^{15}$, halogen, and a heterocycloalkenyl group (i.e., a heterocyclic group that has at least one, and preferably one, double bond in a ring, e.g.,



[0105] examples of the fused ring moiety include, but are not limited to:



[0106] each R^5 and R^6 are the same or different and are independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, cyano, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl group; wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups;

[0107] each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted

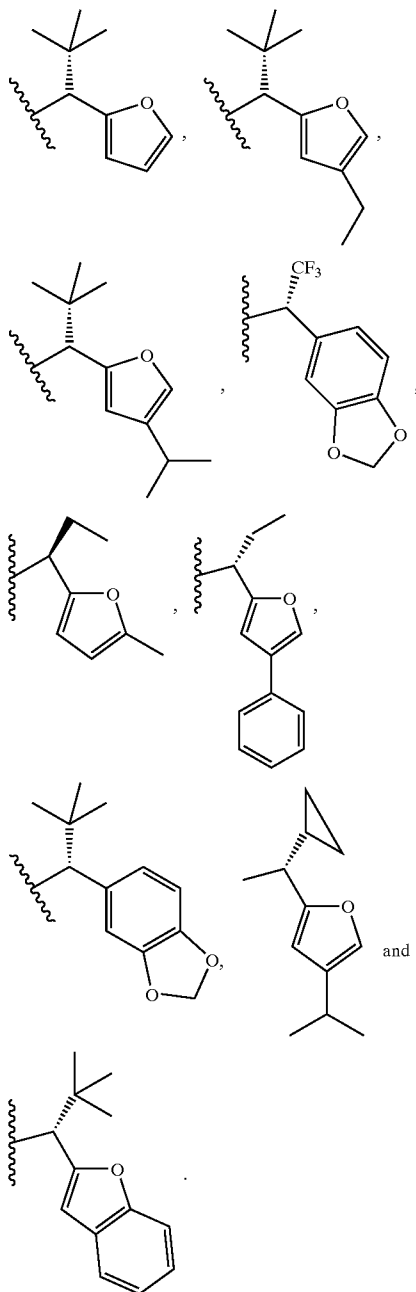
heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, alkynyl, alkenyl, and cycloalkenyl; is and wherein there are one or more (e.g., 1 to 6) substituents on said substituted R^7 and R^8 groups, wherein each substituent is independently selected from the group consisting of:

- [0108] a) halogen,
- [0109] b) $-CF_3$,
- [0110] c) $-COR^{13}$,
- [0111] d) $-OR^{13}$,
- [0112] e) $-NR^{13}R^{14}$,
- [0113] f) $-NO_2$,
- [0114] g) $-CN$,
- [0115] h) $-SO_2OR^{13}$,
- [0116] i) $-Si(alkyl)_3$, wherein each alkyl is independently selected,
- [0117] j) $-Si(aryl)_3$, wherein each alkyl is independently selected,
- [0118] k) $-(R^{13})_2R^{14}Si$, wherein each R^{13} is independently selected,
- [0119] l) $-CO_2R^{13}$,
- [0120] m) $-C(O)NR^{13}R^{14}$,
- [0121] n) $-SO_2NR^{13}R^{14}$,
- [0122] o) $-SO_2R^{13}$,
- [0123] p) $-OC(O)R^{13}$,
- [0124] q) $-OC(O)NR^{13}R^{14}$,
- [0125] r) $-NR^{13}C(O)R^{14}$, and
- [0126] s) $-NR^{13}CO_2R^{14}$;

[0127] (fluoroalkyl is one non-limiting example of an alkyl group that is substituted with halogen);

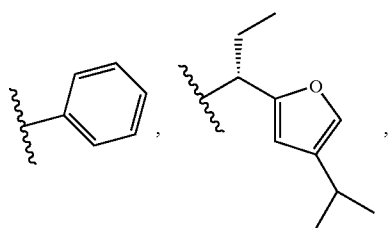
[0128]

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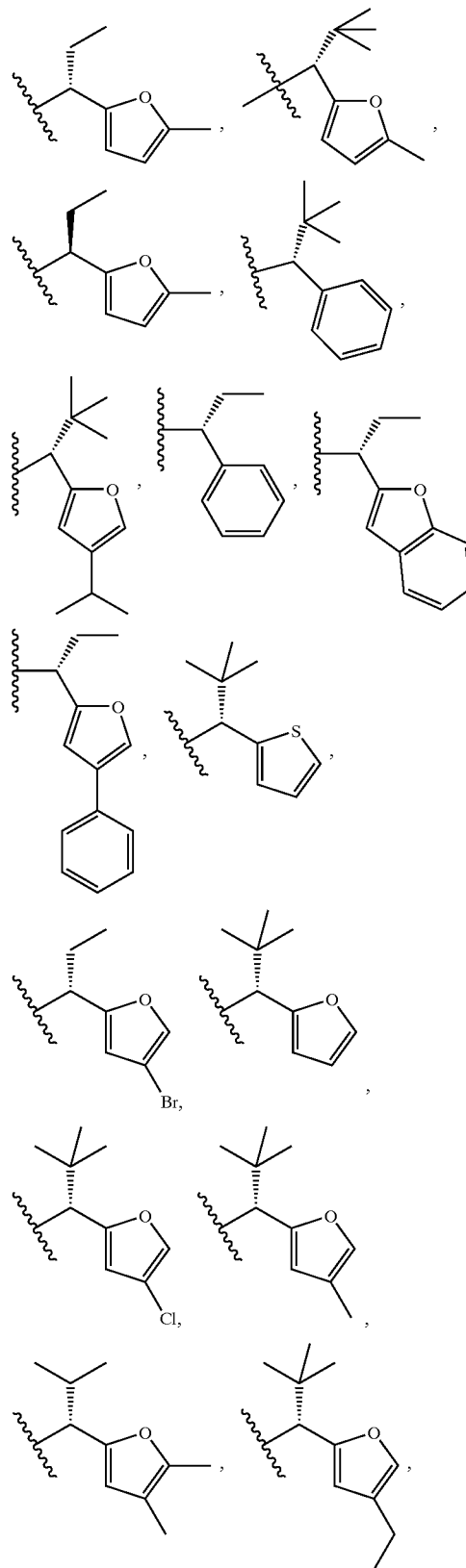


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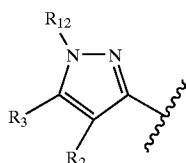
[0175] Substituent A in formula IA is most preferably selected from the group consisting of:



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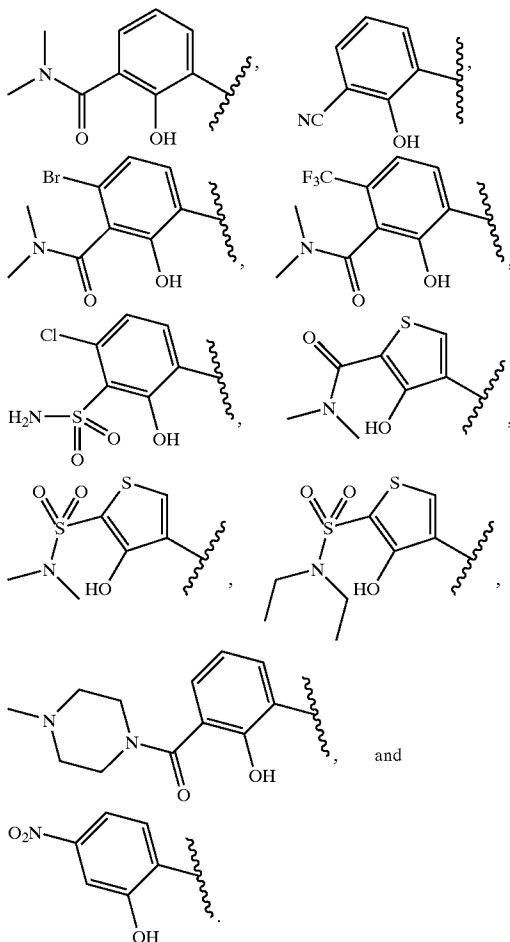


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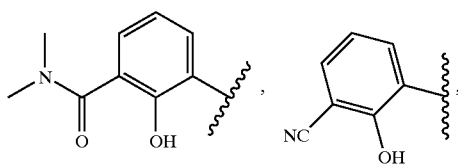


[0179] wherein all substituents are as defined for formula IA.

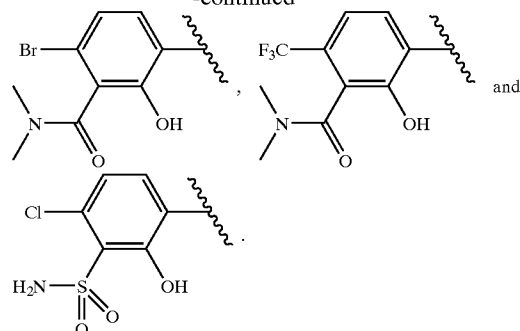
[0180] Substituent B in formula IA is most preferably selected from the group consisting of:



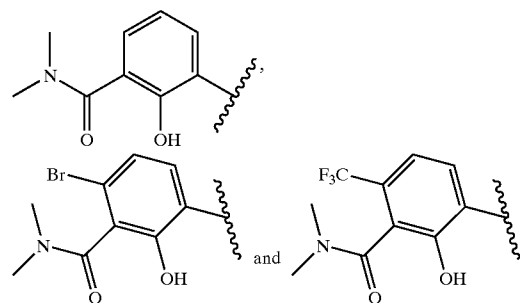
[0181] Substituent B in Formula IA is more preferably selected from the group consisting of:



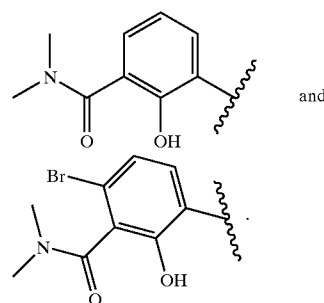
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[0182] Substituent B in Formula IA is even more preferably selected from the group consisting of:



[0183] Substituent B in Formula IA is still even more preferably selected from the group consisting of:

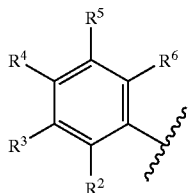


[0184] An embodiment of the present invention is directed to a method of treating an chemokine mediated disease in a patient in need of such treatment (e.g., a mammal, preferably a human being) comprising administering to said patient a therapeutically effective amount of at least one (e.g., 1-3, and usually one) compound of formula IA, or a pharmaceutically acceptable salt or solvate thereof.

[0185] Examples of chemokine mediated (e.g., CXCR1 and/or CXCR2, or CCR7) diseases or conditions include but are not limited to: acute pain, acute inflammation, chronic inflammation, rheumatoid arthritis, acute inflammatory pain, chronic inflammatory pain, neuropathic pain, psoriasis, atopic dermatitis, asthma, COPD, adult respiratory disease,

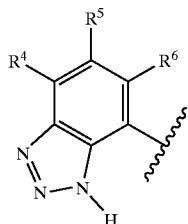
[0196] Representative embodiments of the novel compounds of this invention are described below. The embodiments have been numbered for purposes of reference thereto.

[0197] Embodiment No. 1 is directed to the novel compounds of formula IA wherein B is:



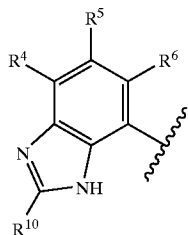
[0198] and all other substituents are as defined for of formula IA.

[0199] Embodiment No. 2 is directed to the novel compounds of formula IA wherein B is:

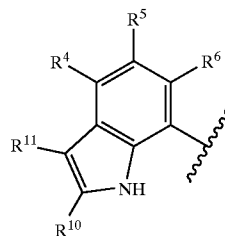


[0200] and all other substituents are as defined for of formula IA.

[0201] Embodiment No. 3 is directed to the novel compounds of formula IA wherein B is:

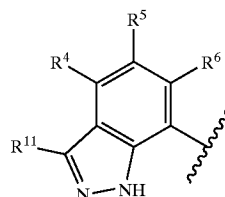


[0202] and all other substituents are as defined for of formula IA. Embodiment No. 4 is directed to the novel compounds of formula IA wherein B is:



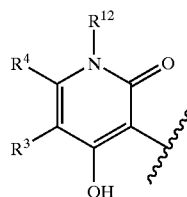
[0203] and all other substituents are as defined for of formula IA.

[0204] Embodiment No. 5 is directed to the novel compounds of formula IA wherein B is:



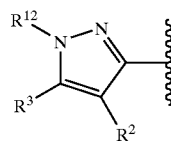
[0205] and all other substituents are as defined for of formula IA.

[0206] Embodiment No. 6 is directed to the novel compounds of formula IA wherein B is:



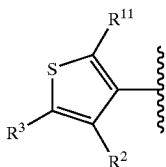
[0207] and all other substituents are as defined for of formula IA.

[0208] Embodiment No. 7 is directed to the novel compounds of formula IA wherein B is:



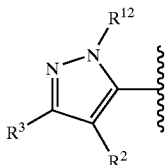
[0209] and all other substituents are as defined for of formula IA.

[0210] Embodiment No. 8 is directed to the novel compounds of formula IA wherein B is:



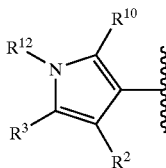
[0211] and all other substituents are as defined for of formula IA.

[0212] Embodiment No. 9 is directed to the novel compounds of formula IA wherein B is:



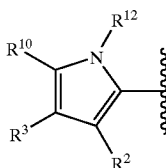
[0213] and all other substituents are as defined for of formula IA.

[0214] Embodiment No. 10 is directed to the novel compounds of formula IA wherein B is:



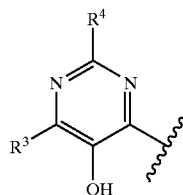
[0215] and all other substituents are as defined for of formula IA.

[0216] Embodiment No. 11 is directed to the novel compounds of formula IA wherein B is:



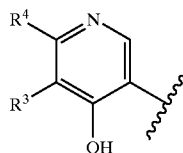
[0217] and all other substituents are as defined for of formula IA.

[0218] Embodiment No. 12 is directed to the novel compounds of formula IA wherein B is:



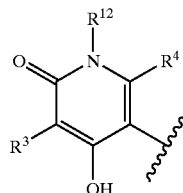
[0219] and all other substituents are as defined for of formula IA.

[0220] Embodiment No. 13 is directed to the novel compounds of formula IA wherein B is:



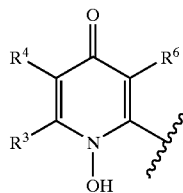
[0221] and all other substituents are as defined for of formula IA.

[0222] Embodiment No. 14 is directed to the novel compounds of formula IA wherein B is:



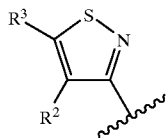
[0223] and all other substituents are as defined for of formula IA.

[0224] Embodiment No. 15 is directed to the novel compounds of formula IA wherein B is:



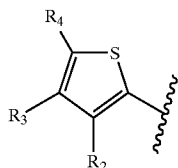
[0225] and all other substituents are as defined for of formula IA.

[0226] Embodiment No. 16 is directed to the novel compounds of formula IA wherein B is:



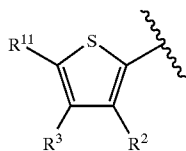
[0227] and all other substituents are as defined for formula IA.

[0228] Embodiment No. 17 is directed to the novel compounds of formula IA wherein B is:



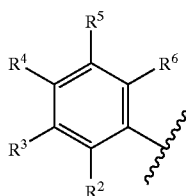
[0229] and all other substituents are as defined for formula IA.

[0230] Embodiment No. 18 is directed to the novel compounds of formula IA wherein B is:

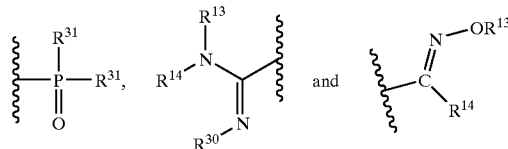


[0231] and all other substituents are as defined for formula IA.

[0232] Embodiment No. 19 is directed to compounds of formula IA wherein B is selected from the group consisting of:

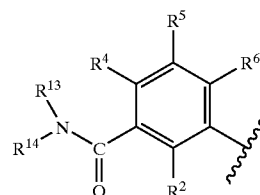


[0233] and R³ for this B group is selected from the group consisting of: —C(O)NR¹³R¹⁴,



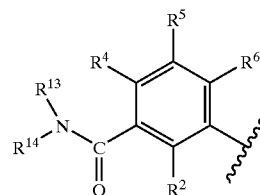
[0234] and all other substituents are as defined for formula IA.

[0235] Embodiment No. 20 is directed to compounds of formula IA wherein B is:



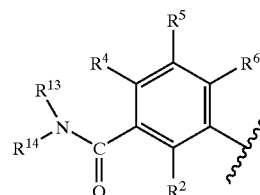
[0236] and all other substituents are as defined in formula IA.

[0237] Embodiment No. 21 is directed to compounds of formula IA wherein B is



[0238] R¹³ and R¹⁴ are independently selected from the group consisting of H and alkyl (e.g., methyl, ethyl, isopropyl and t-butyl), and all other substituents are as defined in formula IA.

[0239] Embodiment No. 22 is directed to compounds of formula IA wherein B is



(1)

[0240] wherein:

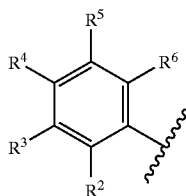
[0241] (1) R² is —OH and all other substituents are as defined in formula IA, or

[0242] (2) R^2 is $-\text{OH}$, and R^{13} and R^{14} are independently selected from the group, consisting of: H and alkyl (e.g., methyl, ethyl, isopropyl and t-butyl), or

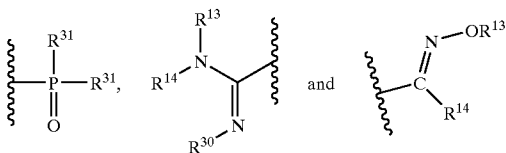
[0243] (3) R^2 is $-\text{OH}$, and R^{13} and R^{14} are the same or different and alkyl group (e.g., methyl, ethyl, isopropyl and t-butyl), for example the same alkyl group, for example methyl, and

[0244] (4) and all other substituents are as defined in formula IA.

[0245] Embodiment No. 23 is directed to compounds of formula IA wherein B is

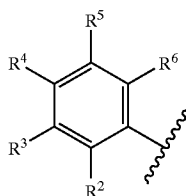


[0246] R^3 is selected from the group consisting of:

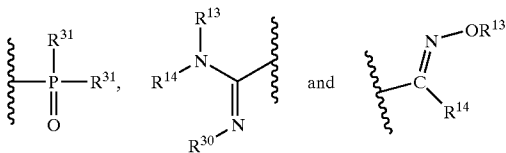


[0247] and all other substituents are as defined in formula IA.

[0248] Embodiment No. 24 is directed to compounds of formula IA wherein B is

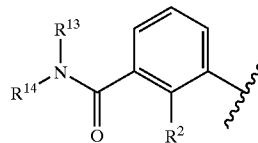


[0249] R^3 is selected from the group consisting of:



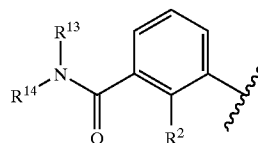
[0250] R^2 is $-\text{OH}$, and all other substituents are as defined in formula IA.

[0251] Embodiment No. 25 is directed to compounds of formula IA wherein B is:



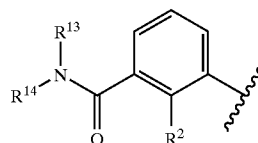
[0252] and all other substituents are as defined in formula IA.

[0253] Embodiment No. 26 is directed to compounds of formula IA wherein B is:



[0254] R^2 is $-\text{OH}$, and all other substituents are as defined in formula IA.

[0255] Embodiment No. 26 is directed to compounds of formula IA wherein B is:



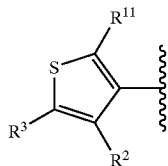
[0256] R^2 is as defined for compounds of formula IA, R^{1

[0259] Embodiment No. 29 is directed to novel compounds of formula IA wherein B is as described in Embodiment No. 23, R^4 is H, R^5 is H, R^6 is H, and all other substituents are as defined for compounds of formula IA.

[0260] Embodiment No. 30 is directed to novel compounds of formula IA wherein B is as described in Embodiment No. 24, R^4 is H, R^5 is H, R^6 is H, and all other substituents are defined for compounds of formula IA.

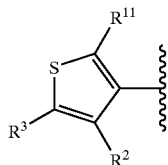
[0261] Embodiment No. 31 is directed to novel compounds of formula IA wherein B is as described in Embodiments Nos. 21, 22, 25 and 26, except that R^{13} and R^{14} are each methyl, and all other substituents are as defined in formula IA.

[0262] Embodiment No. 32 is directed to compounds of formula IA wherein B is:



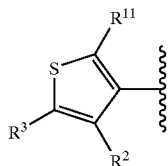
[0263] R^{11} is H or methyl (preferably H), and all other substituents are as defined in formula IA.

[0264] Embodiment No. 33 is directed to compounds of formula IA wherein B is:



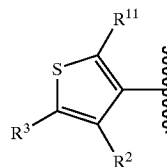
[0265] R^2 is $-\text{OH}$, and all other substituents are as defined in formula IA.

[0266] Embodiment No. 34 is directed to compounds of formula IA wherein B is:



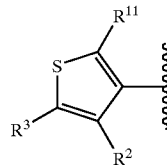
[0267] R^3 is $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, and all other substituents are as defined in formula IA.

[0268] Embodiment No. 35 is directed to compounds of formula IA wherein B is:



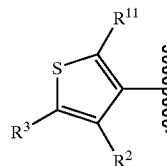
[0269] R^3 is $-\text{S}(\text{O})_t\text{NR}^{13}\text{R}^{14}$ (e.g., t is 2), and all other substituents are as defined in formula IA.

[0270] Embodiment No. 36 is directed to compounds of formula IA wherein B is:



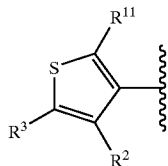
[0271] R^2 is $-\text{OH}$, R^3 is $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, and all other substituents are as defined in formula IA.

[0272] Embodiment No. 37 of this invention is directed to compounds of formula IA wherein B is:



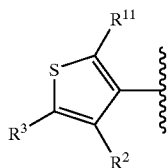
[0273] R^2 is $-\text{OH}$, and R^3 is $-\text{S}(\text{O})_t\text{NR}^{13}\text{R}^{14}$ (e.g., t is 2), and all other substituents are as defined in formula IA.

[0276] Embodiment No. 39 is directed to compounds of formula IA wherein B is:

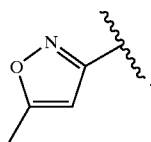


[0277] R² is —OH, R³ is —S(O)_tNR¹³R¹⁴ (e.g., t is 2), R¹¹ is H or methyl (preferably H), and all other substituents are as defined in formula IA.

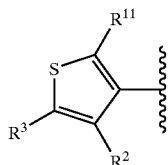
[0278] Embodiment No. 40 is directed to compounds of formula IA wherein B is:



[0279] R² is —OH, R³ is —C(O)NR¹³R¹⁴, R¹¹ is H or methyl (preferably H), and R¹³ and R¹⁴ are independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, isopropyl and t-butyl), unsubstituted cycloalkyl, substituted cycloalkyl, unsubstituted heteroaryl and substituted heteroaryl, and all other substituents are as defined in formula IA. For example, one of R¹³ or R¹⁴ is alkyl (e.g., methyl). An example of a substituted heteroaryl group is



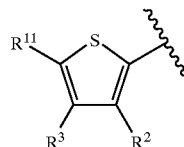
[0280] Embodiment No. 41 is directed to compounds of formula IA wherein B is:



[0281] R² is —OH, R³ is —S(O)_tNR¹³R¹⁴ (e.g., t is 2), R¹¹ is H or methyl (preferably H), and R¹³ and R¹⁴ are independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, isopropyl, and t-butyl), unsubstituted cycloalkyl, and substituted cycloalkyl, and all other substituents are as defined in formula IA. For example R³ is (1) —SO₂NH₂ or (2) —SO₂NR¹³R¹⁴ wherein R¹³ and R¹⁴ are

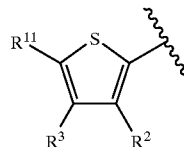
the same or different alkyl group (e.g., methyl, ethyl, isopropyl and t-butyl), e.g., the same alkyl group, such as, for example —SO₂N(CH₃)₂.

[0282] Embodiment No. 42 is directed to compounds of formula IA wherein B is:



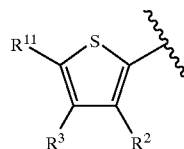
[0283] R¹¹ is H, and all other substituents are as defined in formula IA.

[0284] Embodiment No. 43 is directed to compounds of formula IA wherein B is:

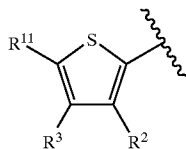


[0285] R² is —OH, and all other substituents are as defined in formula IA.

[0286] Embodiment No. 44 is directed to compounds of formula IA wherein B is:

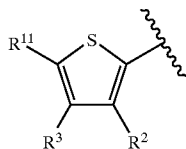


[0290] Embodiment No. 46 is directed to compounds of formula IA wherein B is:



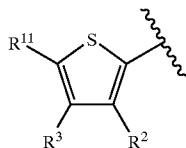
[0291] R² is —OH, R³ is —C(O)NR¹³R¹⁴, and all other substituents are as defined in formula IA.

[0292] Embodiment No. 47 of this invention is directed to compounds of formula IA wherein B is:



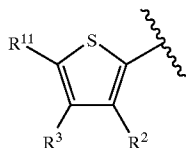
[0293] R² is —OH, and R³ is —S(O)_tNR¹³R¹⁴ (e.g., t is 2), and all other substituents are as defined in formula IA.

[0294] Embodiment No. 48 is directed to compounds of formula IA wherein B is:



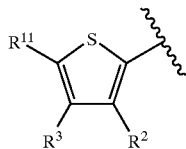
[0295] R² is —OH, R³ is —C(O)NR¹³R¹⁴, R¹¹ is H, and all other substituents are as defined in formula IA.

[0296] Embodiment No. 49 is directed to compounds of formula IA wherein B is:

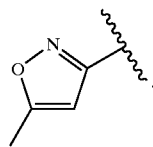


[0297] R² is —OH, R³ is —S(O)_tNR¹³R¹⁴ (e.g., t is 2), R¹¹ is H, and all other substituents are as defined in formula IA.

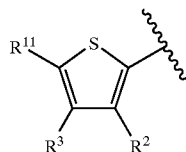
[0298] Embodiment No. 50 is directed to compounds of formula IA wherein B is:



[0299] R² is —OH, R³ is —C(O)NR¹³R¹⁴, R¹¹ is H, and R¹³ and R¹⁴ are independently selected from the group consisting of: alkyl, unsubstituted heteroaryl and substituted heteroaryl, and all other substituents are as defined in formula IA. For example, one of R¹³ or R¹⁴ is alkyl (e.g., methyl). An example of a substituted heteroaryl group is

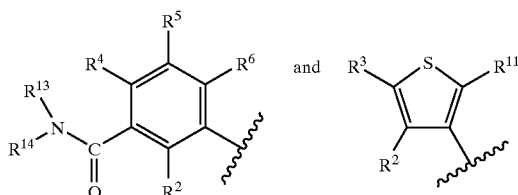


[0300] Embodiment No. 51 is directed to compounds of formula IA wherein B is:



[0301] R² is —OH, R³ is —S(O)_tNR¹³R¹⁴ (e.g., t is 2), R¹¹ is H, R¹³ and R¹⁴ are independently selected from the group consisting of: H and alkyl (e.g., methyl, ethyl, isopropyl, and t-butyl), and all other substituents are as defined in formula IA. For example R³ is (1) —SO₂NH₂ and (2) —SO₂NR¹³R¹⁴ wherein R¹³ and R¹⁴ are the same or different alkyl group (e.g., methyl, ethyl, isopropyl and t-butyl), e.g., the same alkyl group, such as, for example —SO₂N(CH₃

[0324] Embodiment No. 55 is directed to compounds of formula IA wherein substituent B is selected from the group consisting of:



[0325] wherein:

[0326] R^2 is selected from the group consisting of: H, OH, —NHC(O)R^{13} and $\text{—NHSO}_2\text{R}^{13}$;

[0327] R^3 is selected from the group consisting of: $\text{—C(O)NR}^{13}\text{R}^{14}$, $\text{—SO}_2\text{NR}^{13}\text{R}^{14}$, —NO_2 , cyano, and $\text{—SO}_2\text{R}^{13}$;

[0328] R^4 is selected from the group consisting of: H, —NO_2 , cyano, —CH_3 or —CF_3 ;

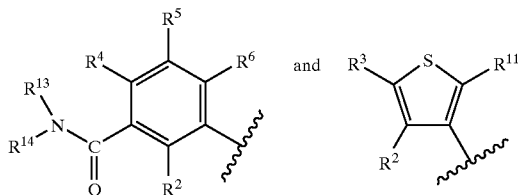
[0329] R^5 is selected from the group consisting of: H, —CF_3 , —NO_2 , halogen and cyano; and

[0330] R^6 is selected from the group consisting of: H, alkyl and —CF_3 ;

[0331] R^{11} is selected from the group consisting of: H, halogen and alkyl; and

[0332] each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl and ethyl.

[0333] Embodiment No. 56 is directed to compounds of formula IA wherein substituent B is selected from the group consisting of:



[0334] wherein:

[0335] R^2 is —OH ;

[0336] R^3 is selected from the group consisting of: $\text{—SO}_2\text{NR}^{13}\text{R}^{14}$ and $\text{—CONR}^{13}\text{R}^{14}$;

[0337] R^4 is selected from the group consisting of: H, —CH_3 and —CF_3 ;

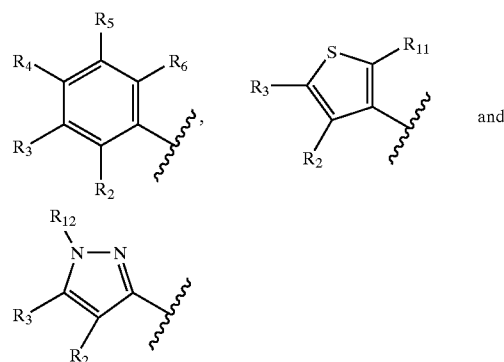
[0338] R^5 is selected from the group consisting of: H and cyano;

[0339] R^6 is selected from the group consisting of: H, —CH_3 and —CF_3 ;

[0340] R^{11} is H; and

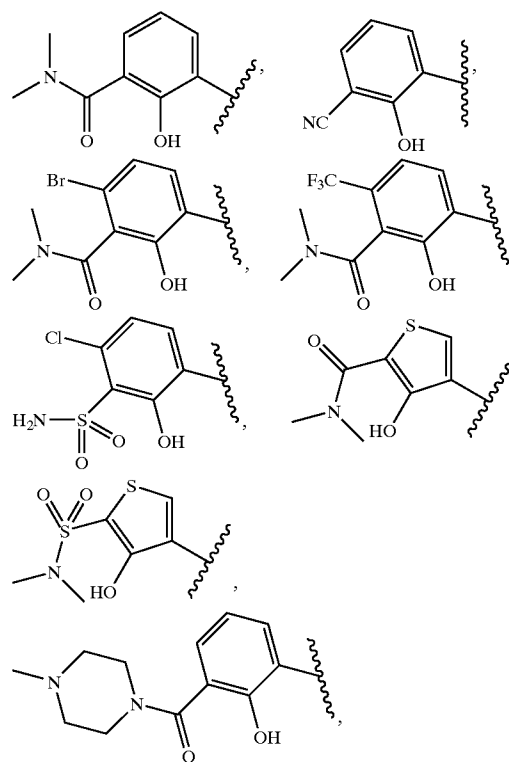
[0341] R^{13} and R^{14} are independently selected from the group consisting of H and methyl (e.g., for $\text{—SO}_2\text{NR}^{13}\text{R}^{14}$ both R^{13} and R^{14} are H, or both R^{13} and R^{14} are methyl, also, for example, for $\text{—CONR}^{13}\text{R}^{14}$ both R^{13} and R^{14} are methyl).

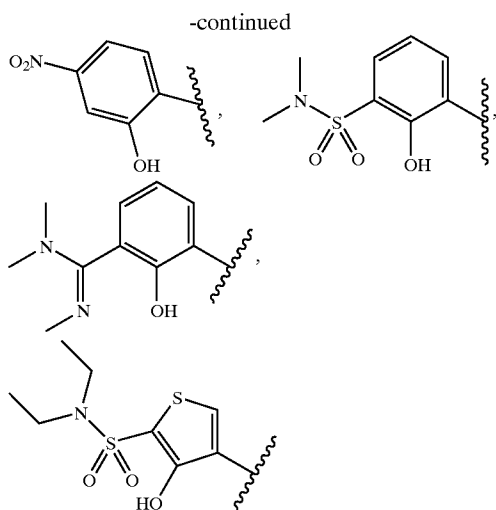
[0342] Embodiment No. 57 is directed to compounds of formula IA wherein substituent B is selected from the group consisting of:



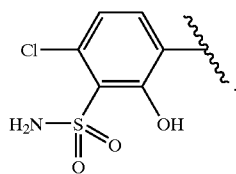
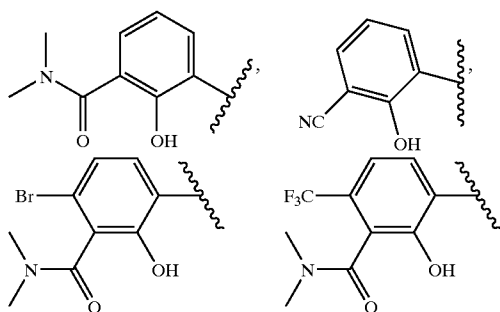
[0343] wherein all substituents are as defined for formula IA.

[0344] Embodiment No. 58 is directed to compounds of formula IA wherein substituent B is selected from the group consisting of:



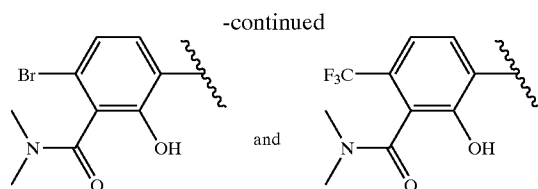
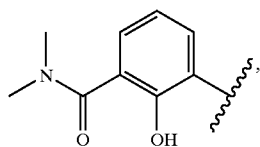


[0345] Embodiment No. 59 is directed to compounds of formula IA wherein substituent B is selected from the group consisting of:

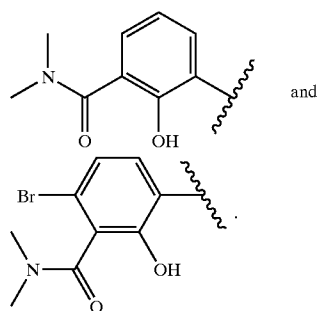


[0346] and

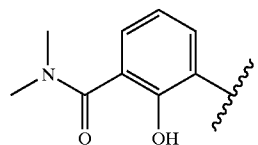
[0347] Embodiment No. 60 is directed to compounds of formula IA wherein substituent B is selected from the group consisting of:



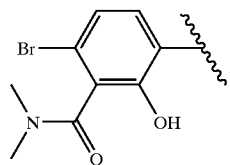
[0348] Embodiment No. 61 is directed to compounds of formula IA wherein substituent B is selected from the group consisting of:



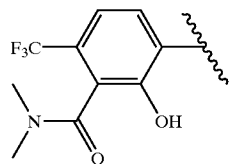
[0349] Embodiment No. 62 is directed to compounds of formula IA wherein substituent B is:



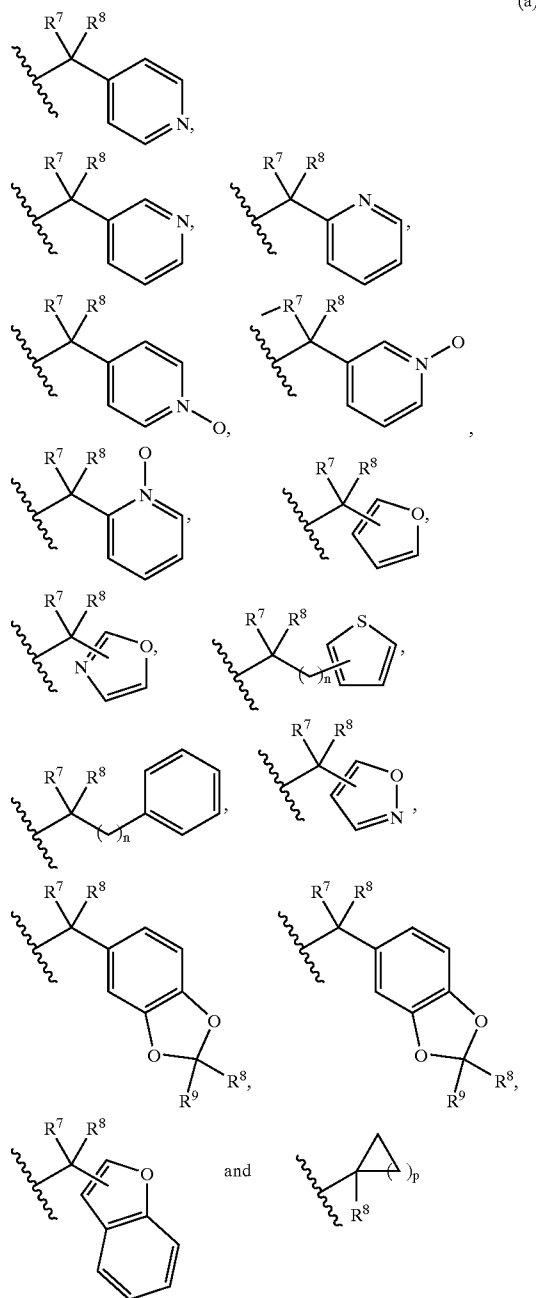
[0350] Embodiment No. 63 is directed to compounds of formula IA wherein substituent B is:



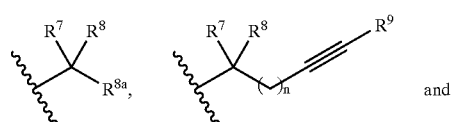
[0351] Embodiment No. 64 is directed to compounds of formula IA wherein substituent B is:



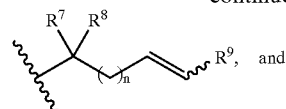
[0352] Embodiment No. 65 is directed to compounds of formula IA wherein: substituent A is selected from the group consisting of:



[0353] wherein the above rings are unsubstituted or substituted, as described for formula IA: and

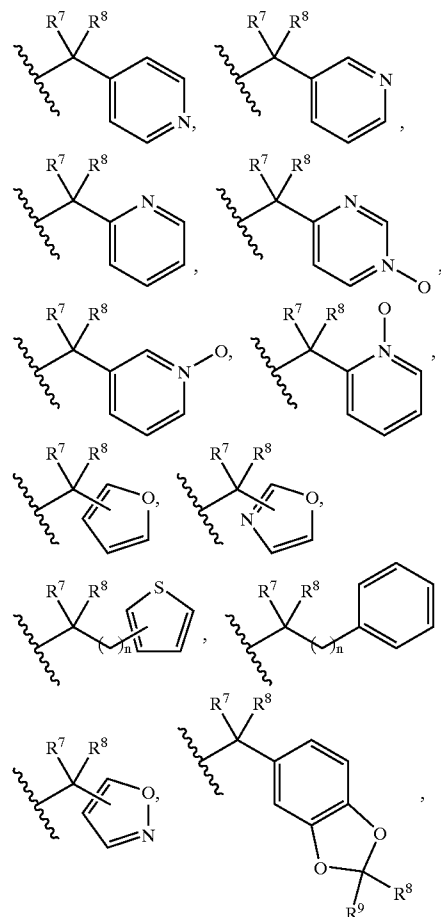


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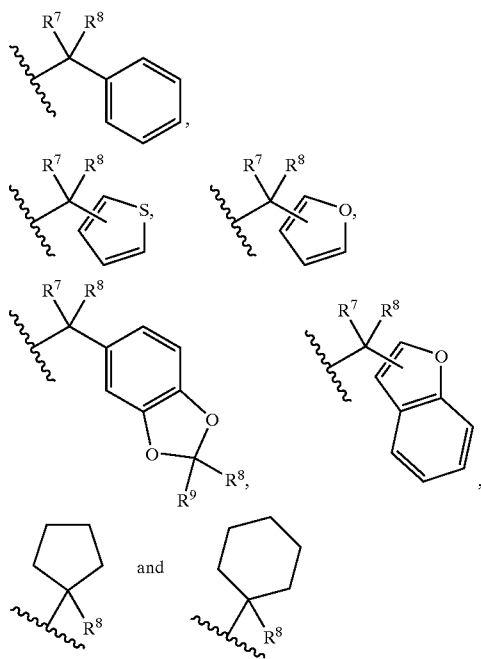


[0354] wherein in (a) and (b): each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, $-\text{CO}_2\text{R}^{13}$, $-\text{CONR}^{13}\text{R}^{14}$, fluoroalkyl, alkynyl, alkenyl, and cycloalkenyl, wherein said substituents on said R^7 and R^8 substituted groups are selected from the group consisting of: a) cyano, b) $-\text{CO}_2\text{R}^{13}$, c) $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, d) $-\text{SO}_2\text{NR}^{13}\text{R}^{14}$, e) $-\text{NO}_2$, f) $-\text{CF}_3$, g) $-\text{OR}^3$, h) $-\text{NR}^{13}\text{R}^{14}$, i) $-\text{OC}(\text{O})\text{R}^{13}$, j) $-\text{OC}(\text{O})\text{NR}^{13}\text{R}^{14}$, and k) halogen; and R^{8a} and R^9 are as defined in formula IA.

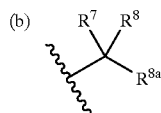
[0355] Embodiment No. 66 is directed to compounds of formula IA wherein substituent A is selected from the group consisting of:



[0361] Embodiment No. 68 is directed to compounds of formula IA wherein substituent A is selected from the group consisting of:

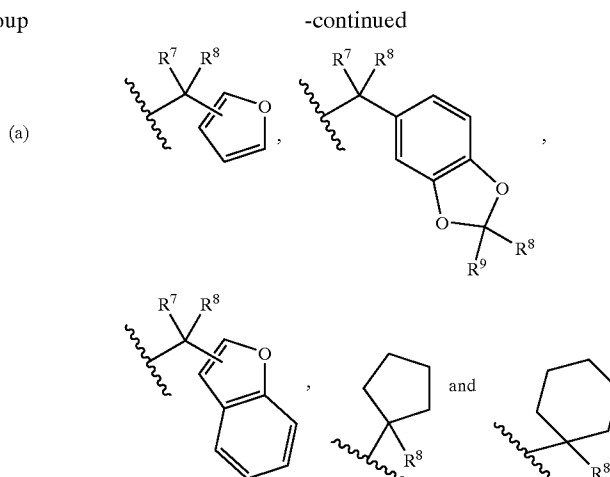
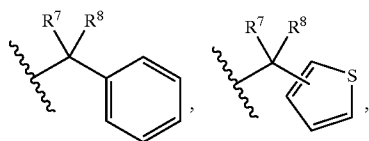


[0362] wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: H, F, Cl, Br, alkyl, cycloalkyl, and $-\text{CF}_3$; R^7 is selected from the group consisting of: H, $-\text{CF}_3$, $-\text{CF}_2\text{CH}_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and

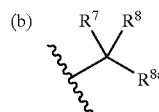


[0363] wherein R^7 is selected from the group consisting of: H, $-\text{CF}_3$, $-\text{CF}_2\text{CH}_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and R^{8a} is as defined for formula IA.

[0364] Embodiment No. 69 is directed compounds of formula IA wherein substituent A is selected from the group consisting of:



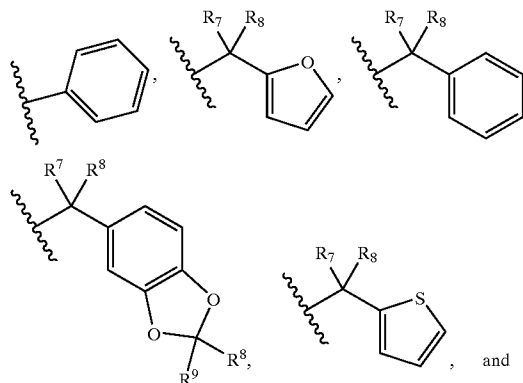
[0365] wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: F, Cl, Br, alkyl, cycloalkyl, and $-\text{CF}_3$; R^7 is selected from the group consisting of: H, $-\text{CF}_3$, $-\text{CF}_2\text{CH}_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and



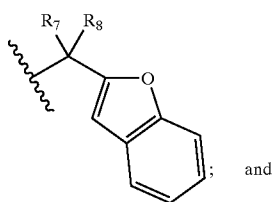
[0366] wherein R^7 is selected from the group consisting of: H, $-\text{CF}_3$, $-\text{CF}_2\text{CH}_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and R^{8a} is as defined for formula IA;

[0367] Embodiment No. 70 is directed compounds of formula IA wherein substituent A is selected from the group consisting of:

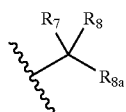
[0368] (1) unsubstituted or substituted:



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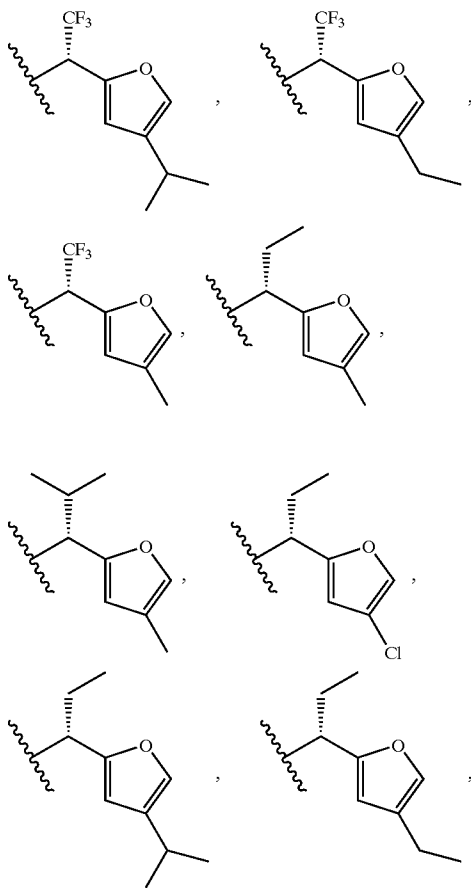


[0369] (2)

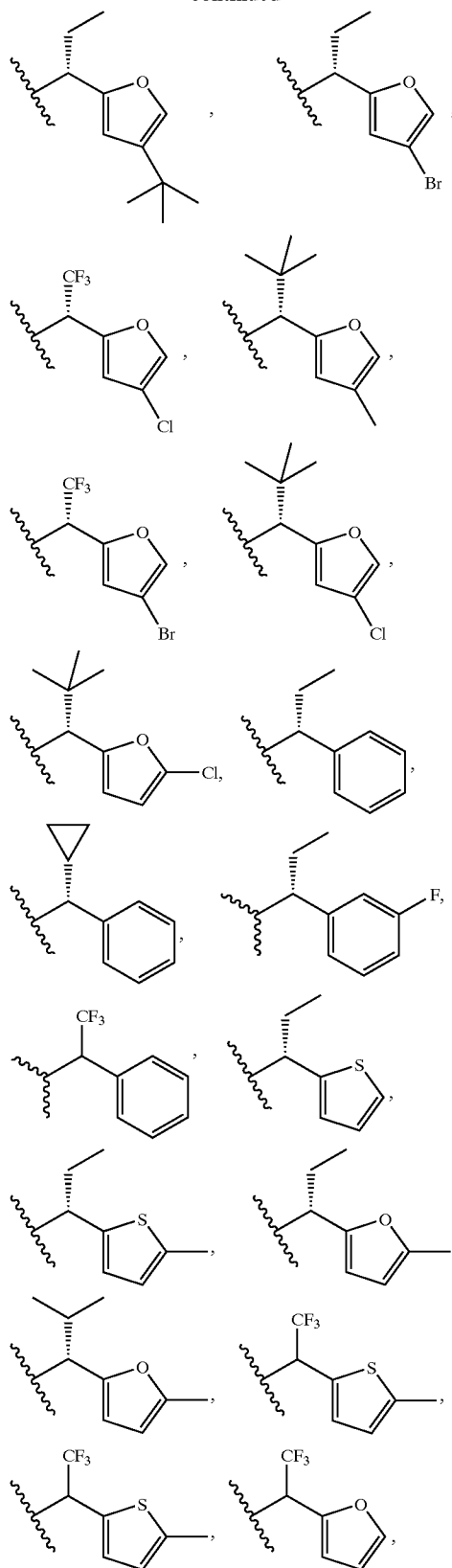


[0370] wherein all substituents are as defined for formula IA.

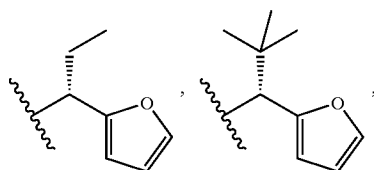
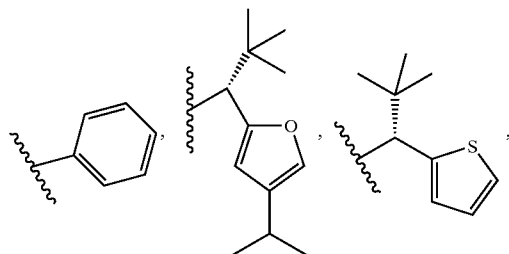
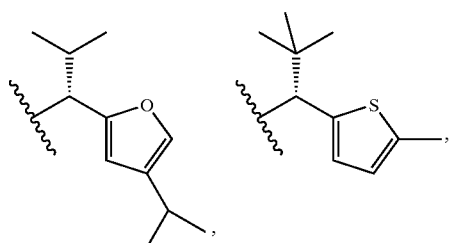
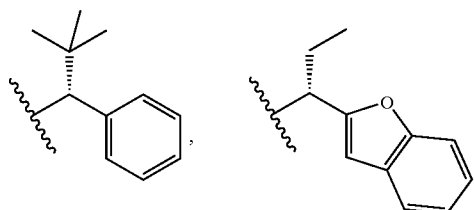
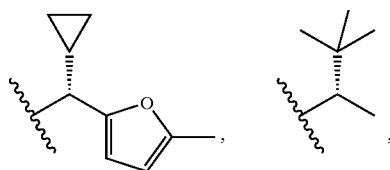
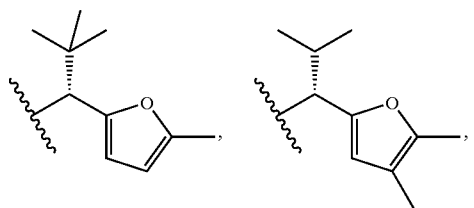
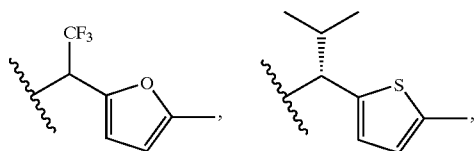
[0371] Embodiment No. 71 is directed to compounds of formula IA wherein substituent A is selected from the group consisting of:



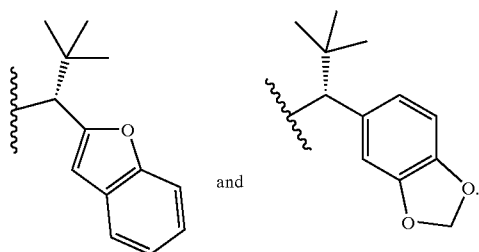
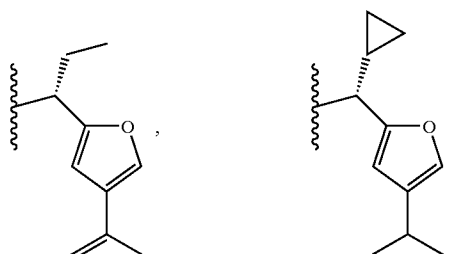
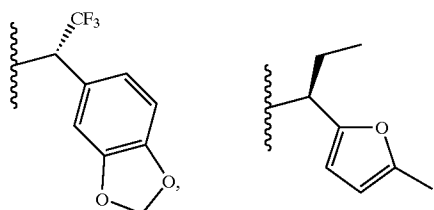
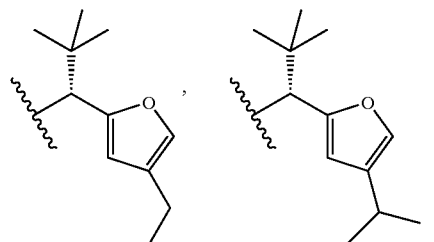
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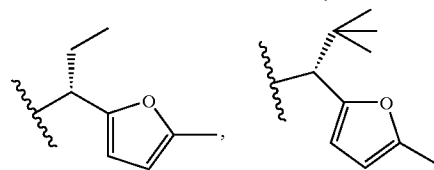
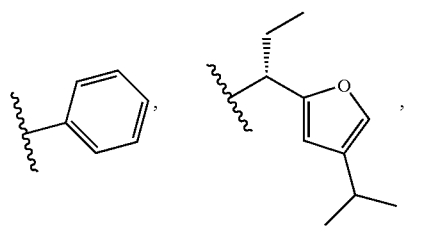


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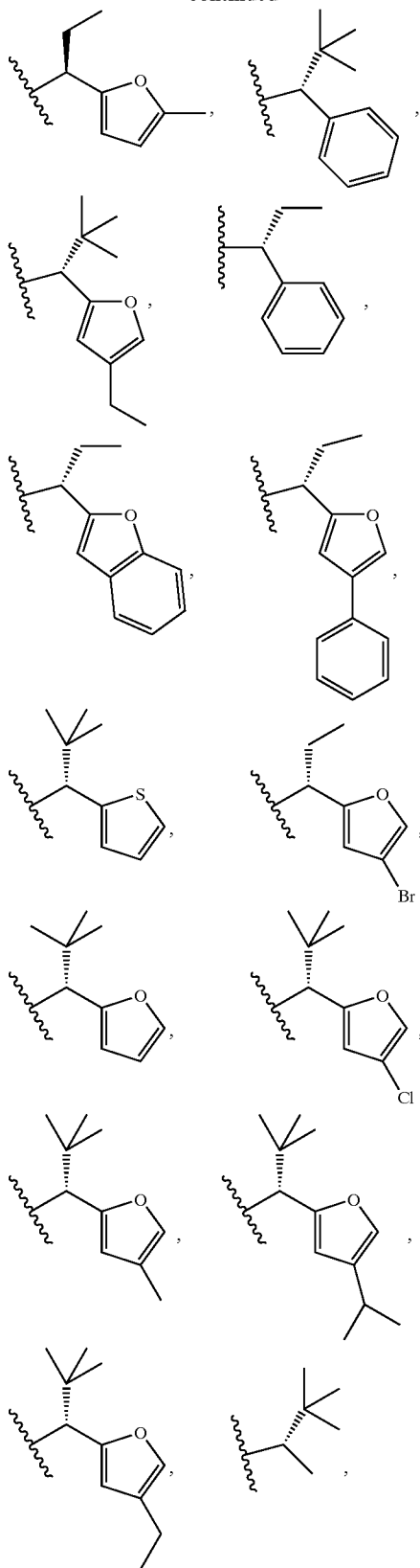


and

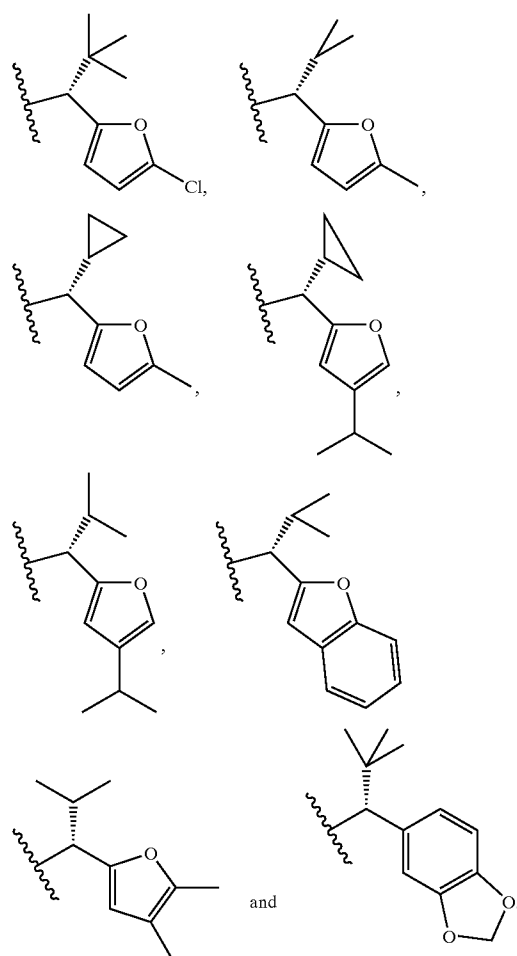
[0372] Embodiment No. 72 is directed to compounds of formula IA wherein substituent A is selected from the group consisting of:



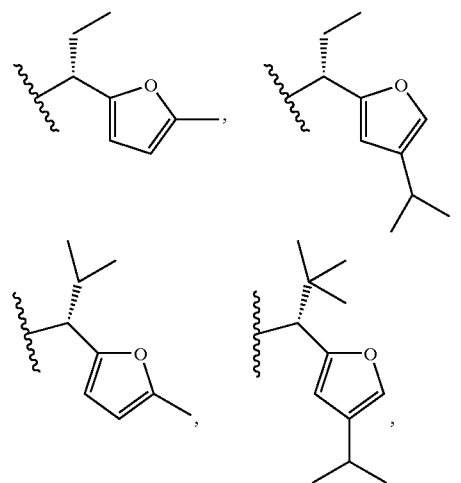
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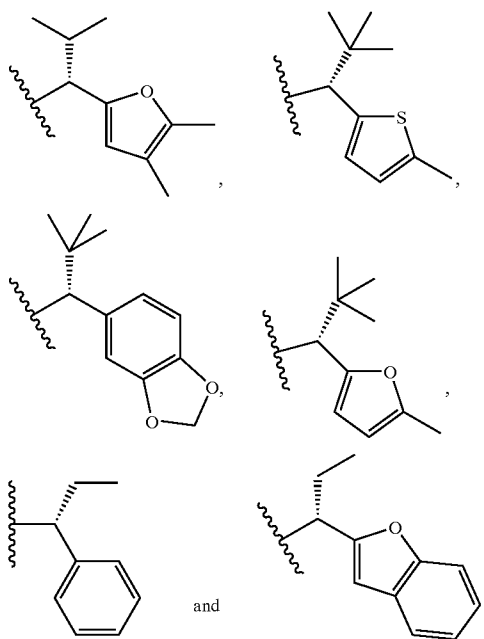
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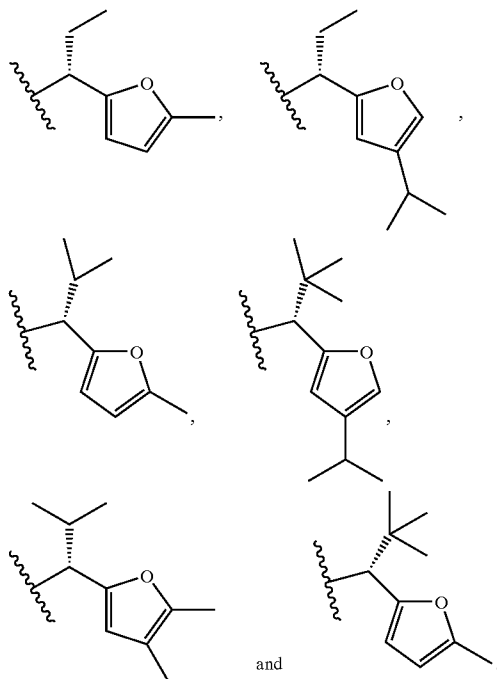
[0373] Embodiment No. 73 is directed to compounds of formula IA wherein substituent A is selected from the group consisting of:



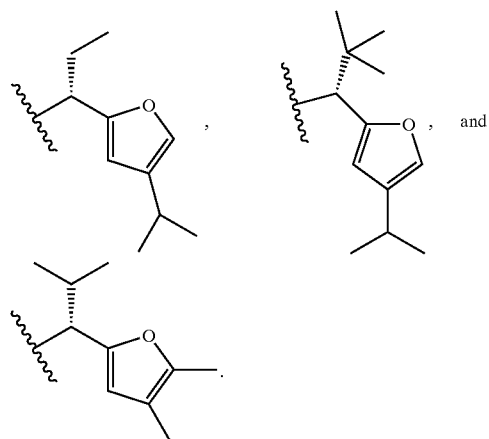
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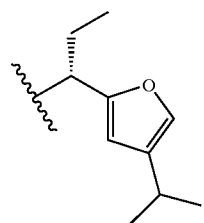
[0374] Embodiment No. 74 is directed to compounds of formula IA wherein substituent A is selected from the group consisting of:



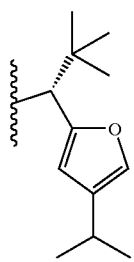
[0375] Embodiment No. 75 is directed to compounds of formula IA wherein substituent A is selected from the group consisting of:



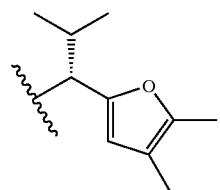
[0376] Embodiment No. 76 is directed to compounds of formula IA wherein substituent A is:



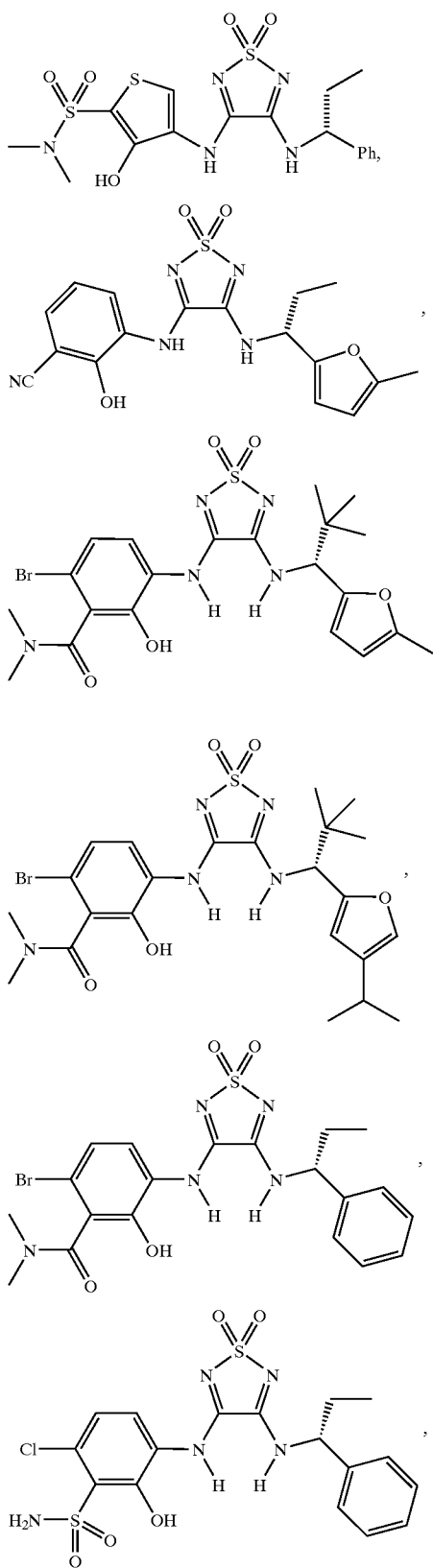
[0377] Embodiment No. 77 is directed to compounds of formula IA wherein substituent A is:



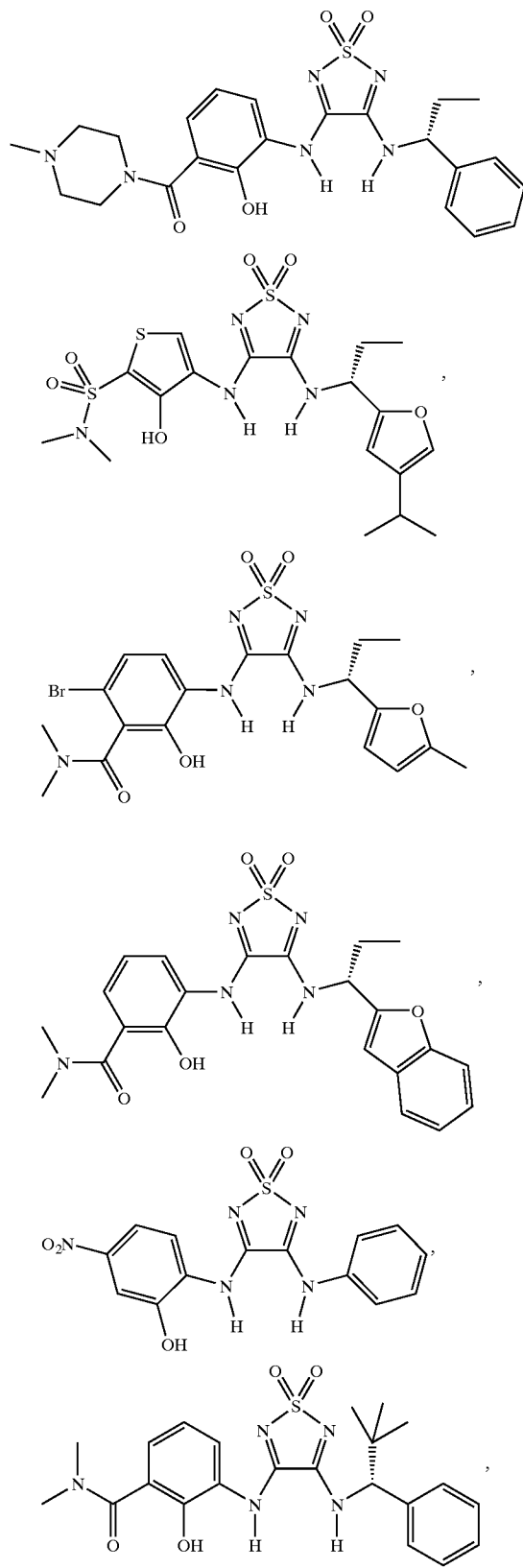
[0378] Embodiment No. 78 is directed to compounds of formula IA wherein substituent A is:



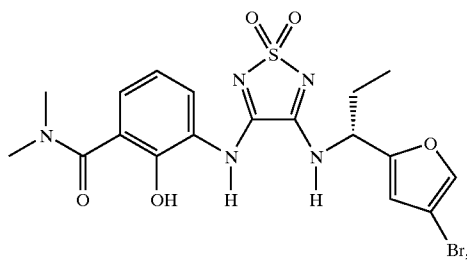
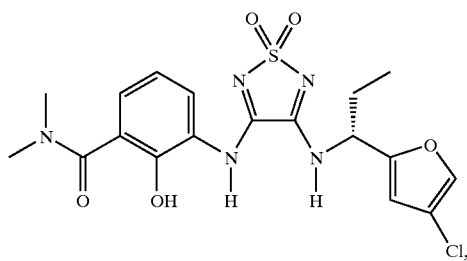
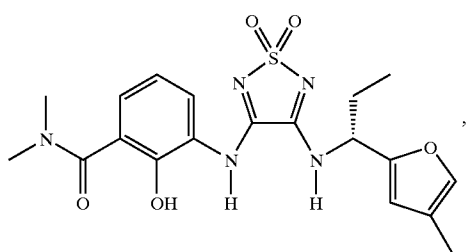
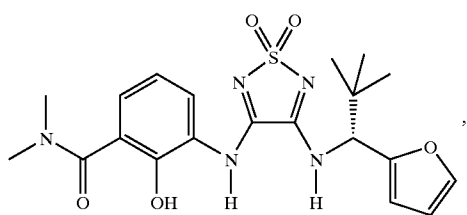
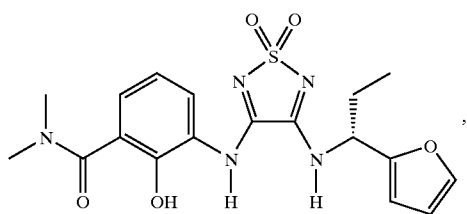
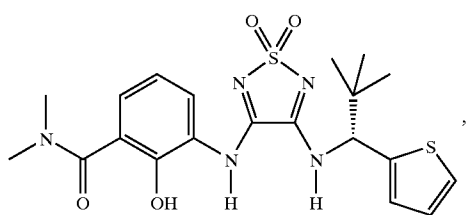
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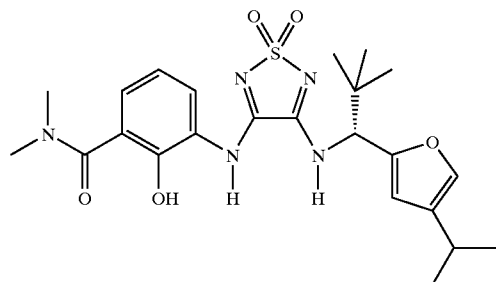
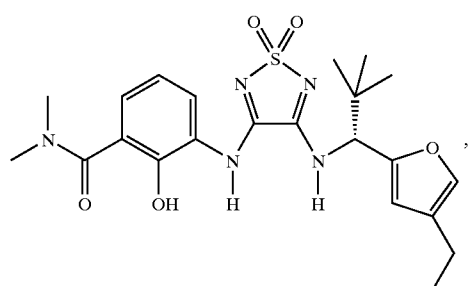
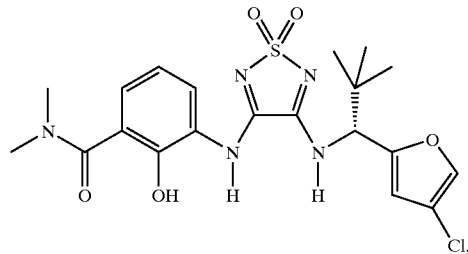
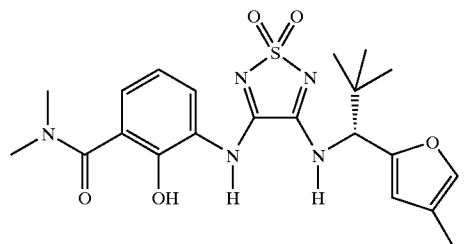
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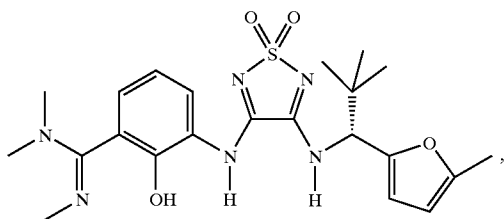
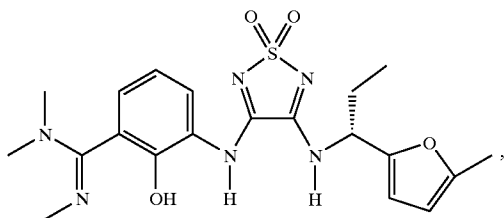
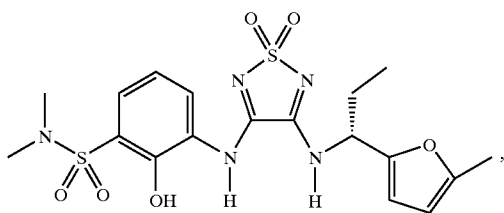
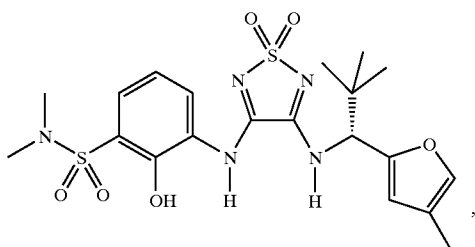
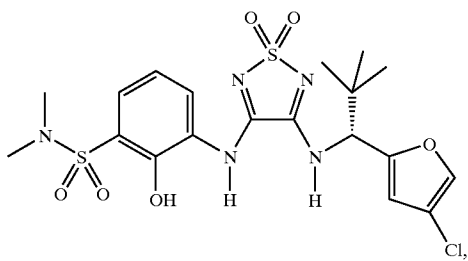
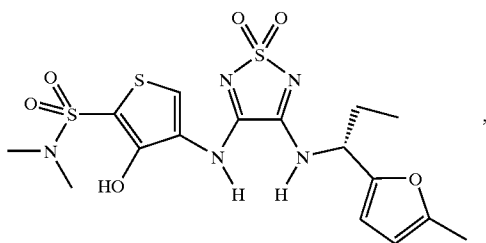
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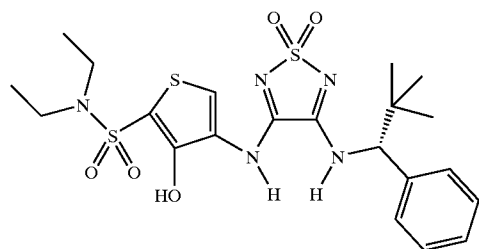
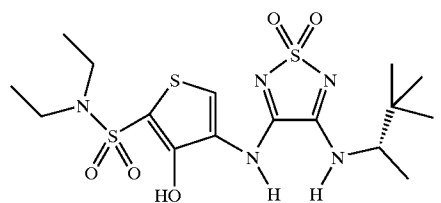
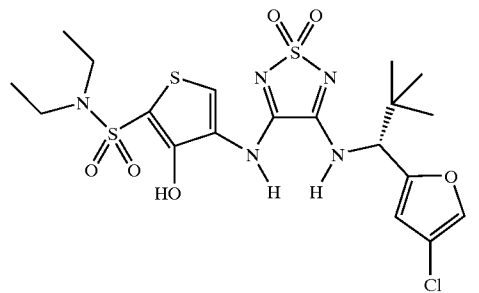
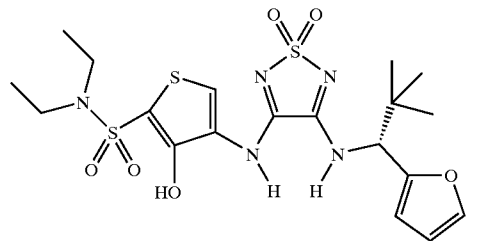
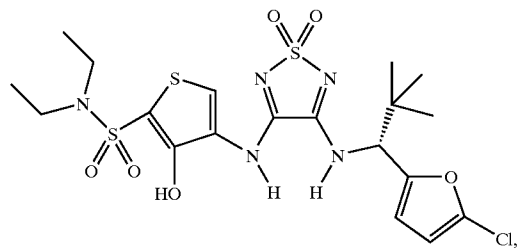
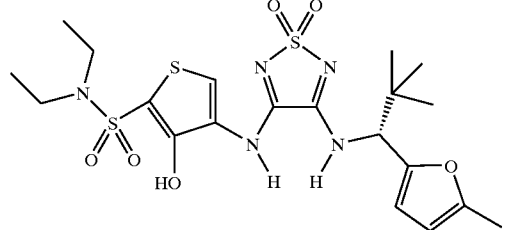
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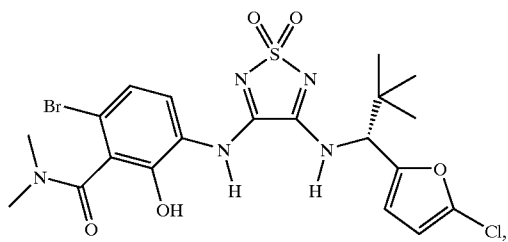
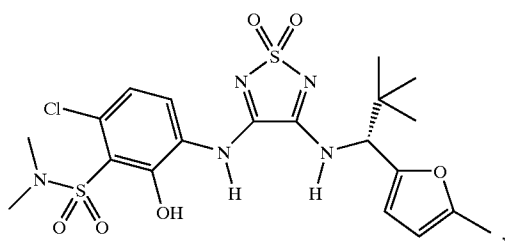
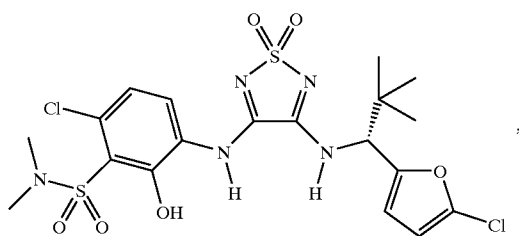
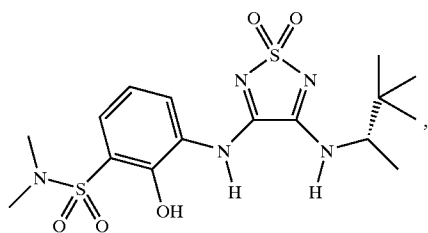
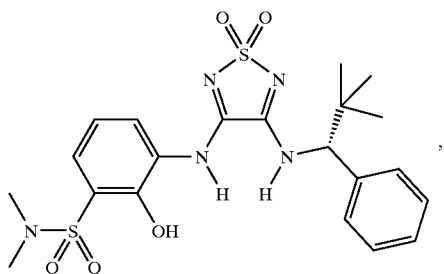
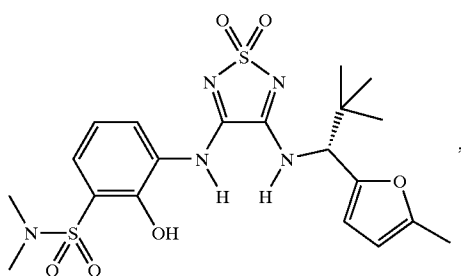
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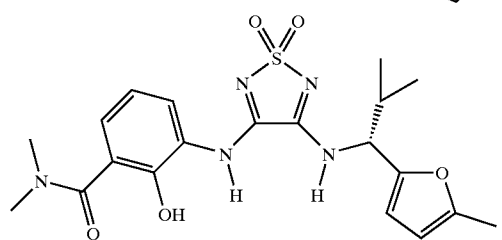
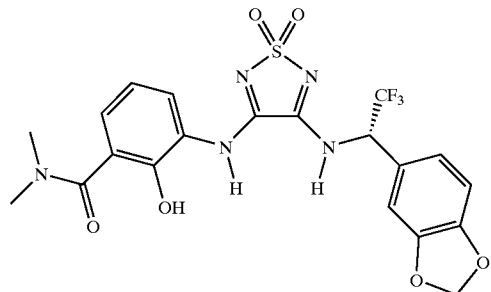
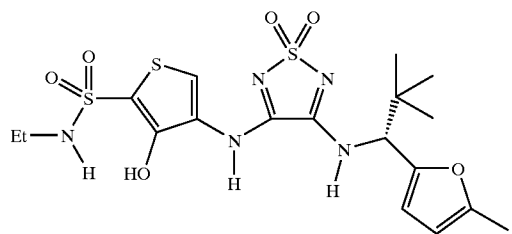
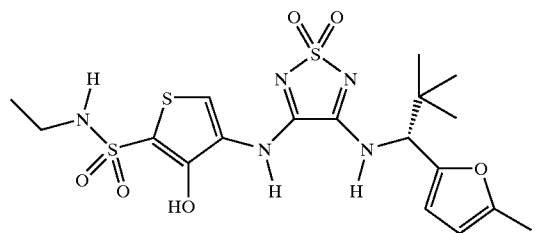
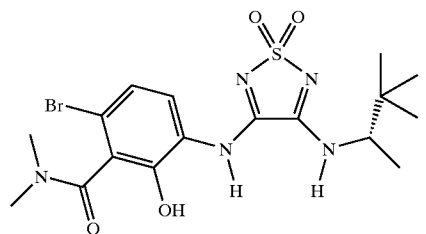
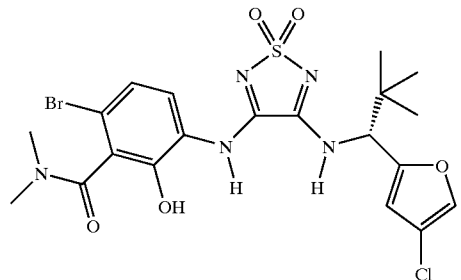
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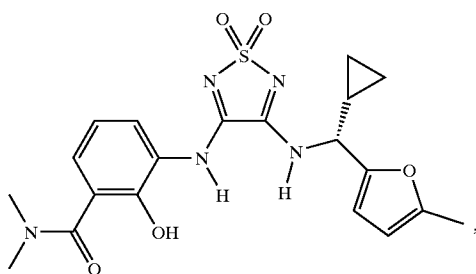
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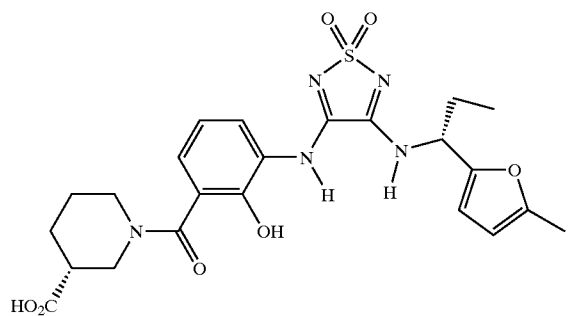
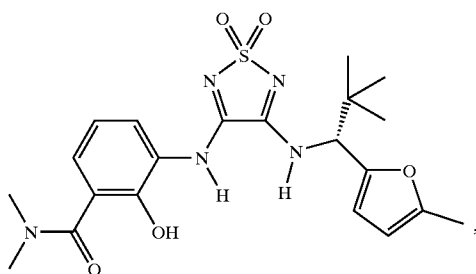
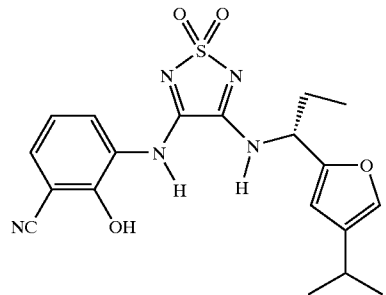
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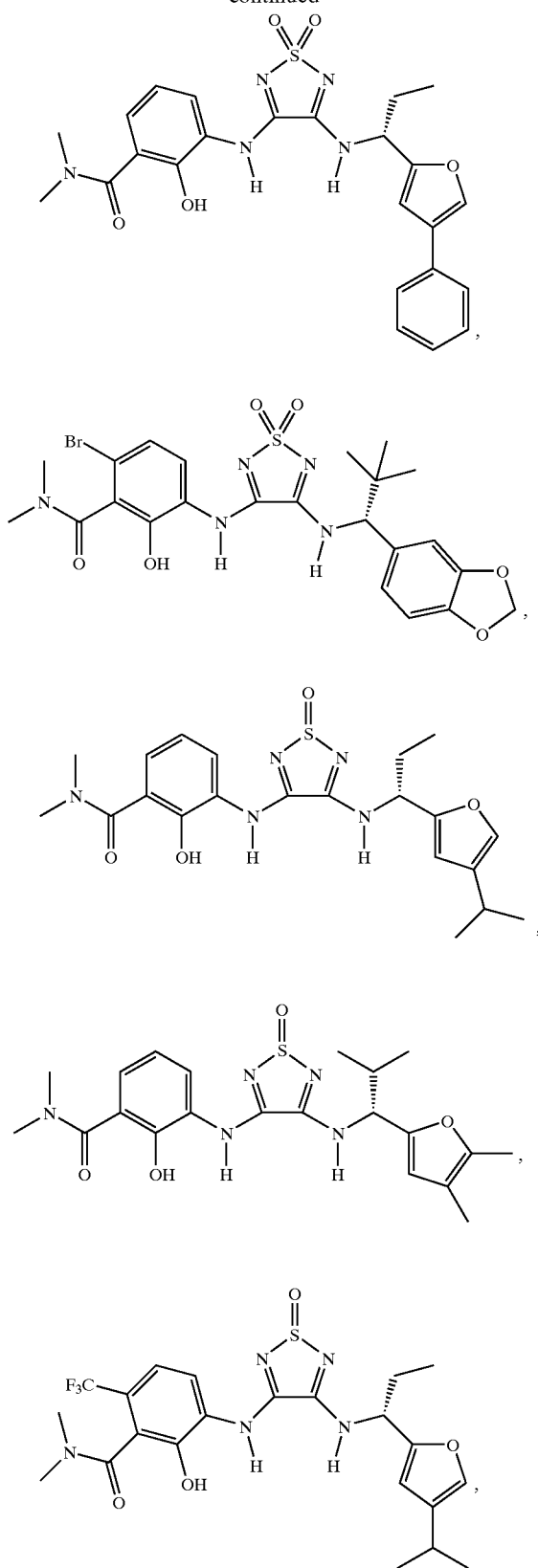
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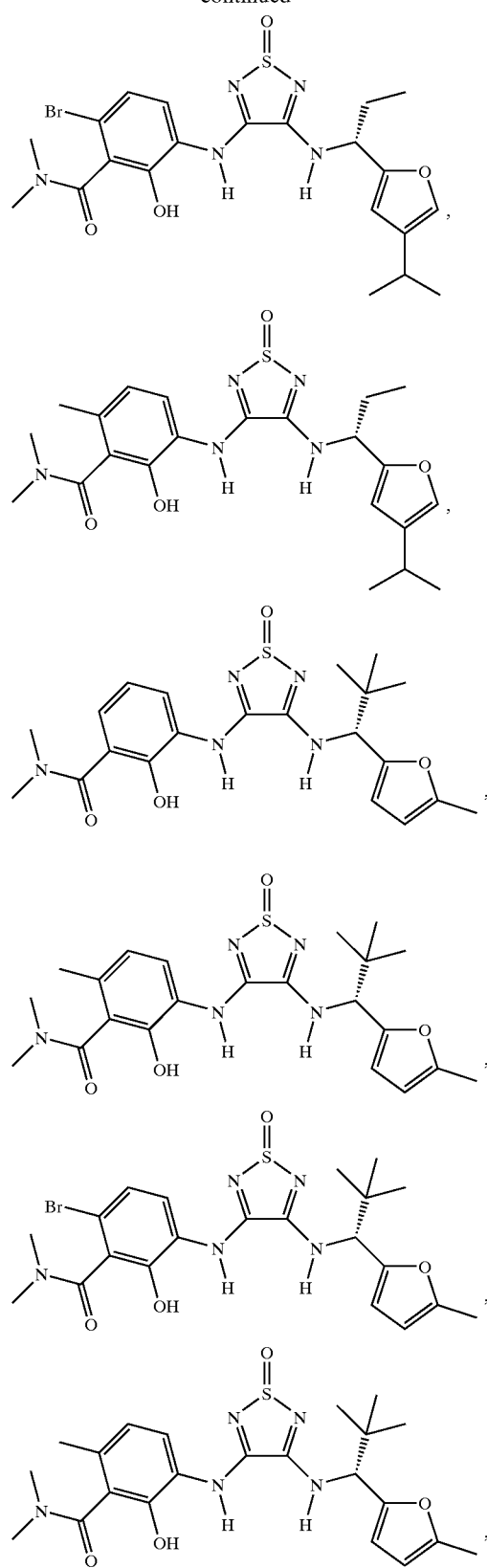
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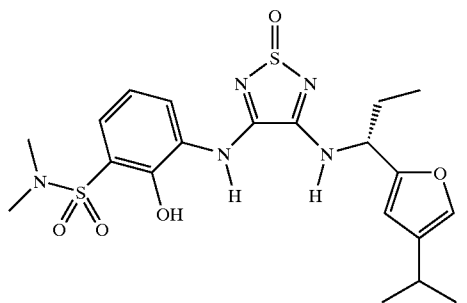
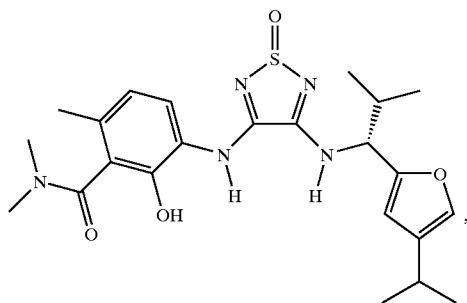
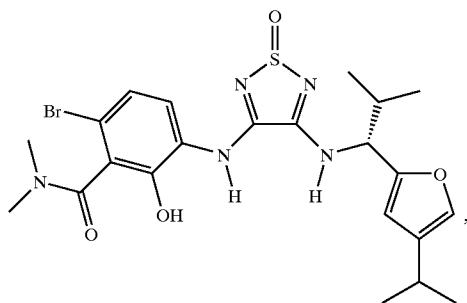
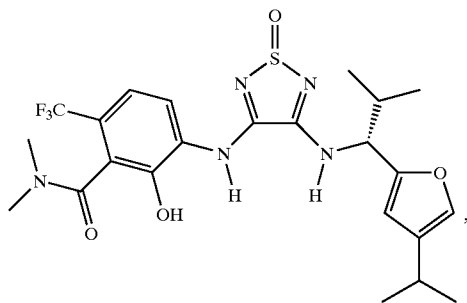
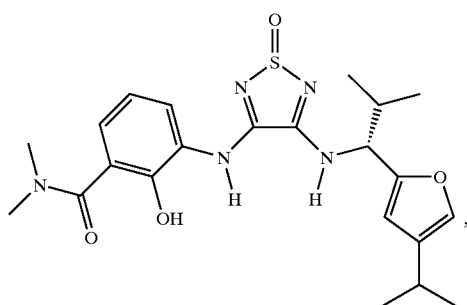
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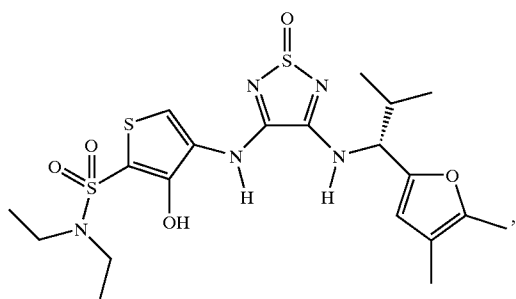
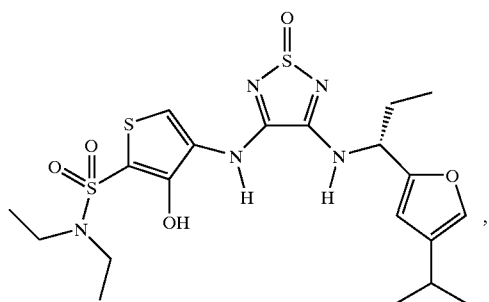
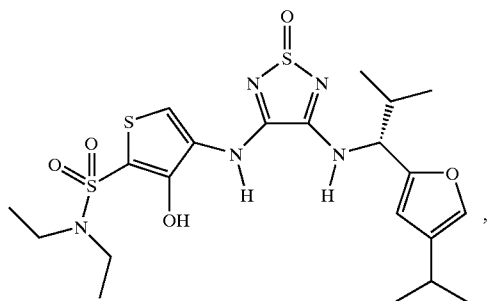
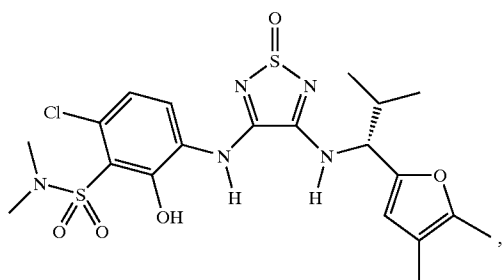
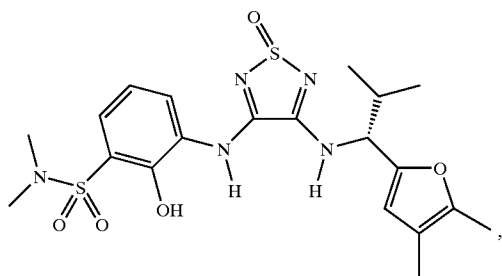
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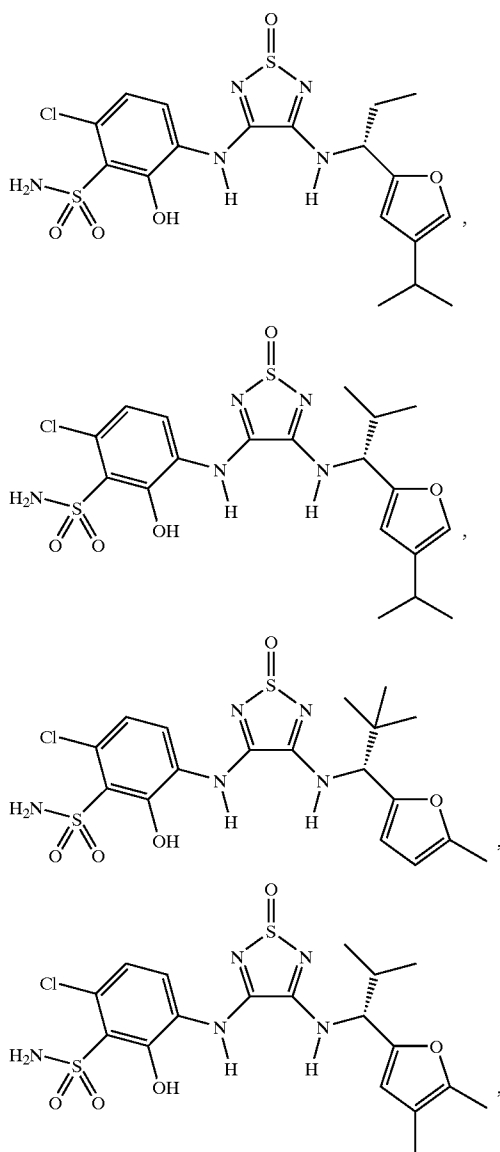
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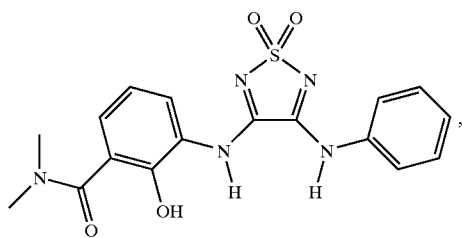


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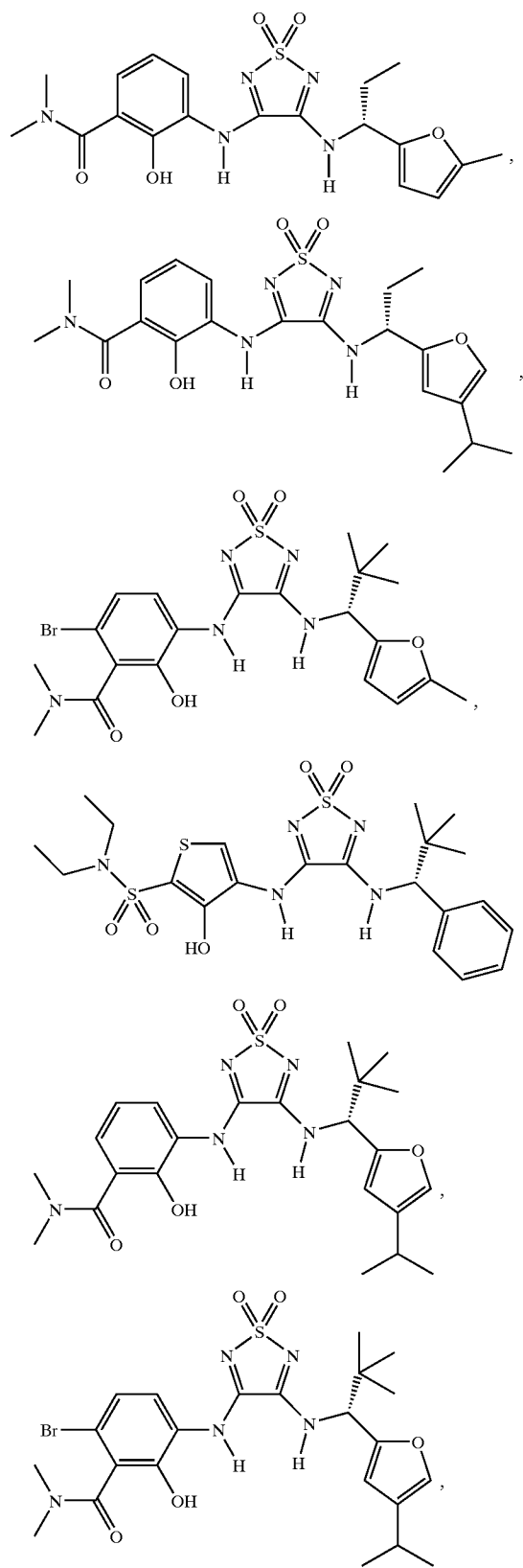


[0507] the pharmaceutically acceptable salts thereof, and the pharmaceutically acceptable solvates thereof.

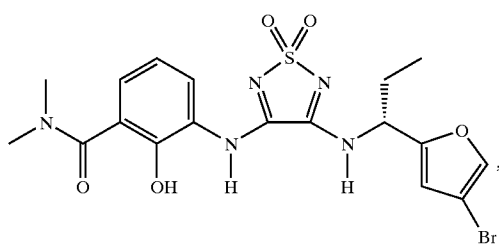
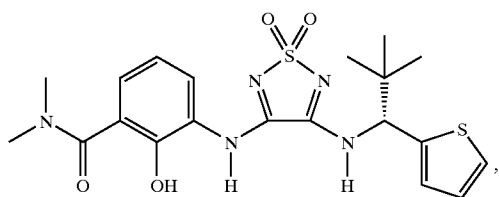
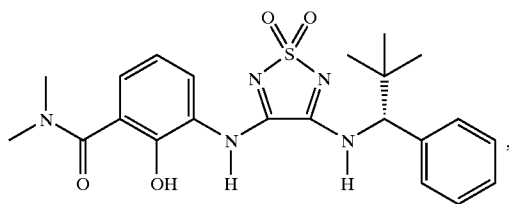
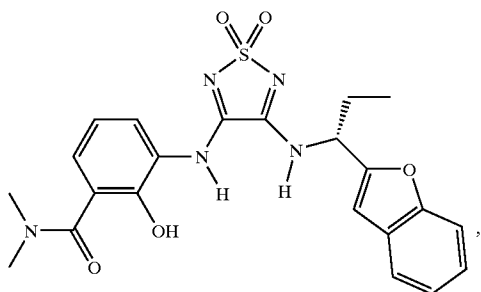
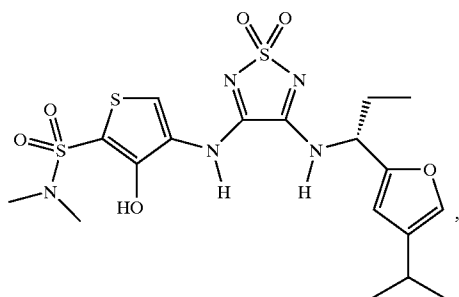
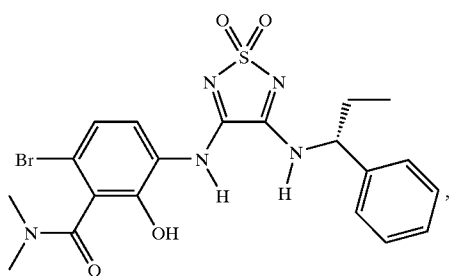
[0508] Preferred compounds of this invention are selected from the group consisting of:



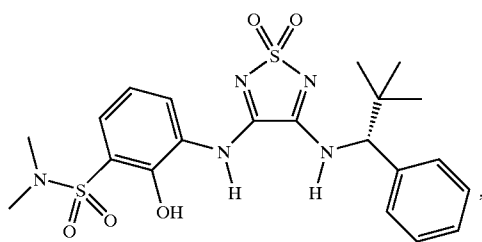
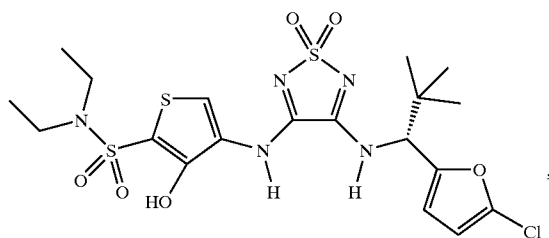
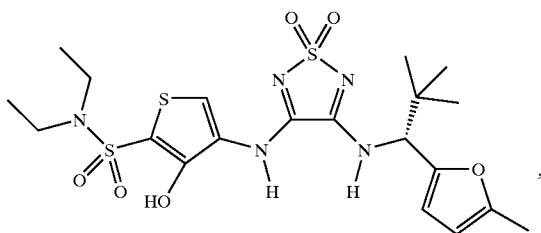
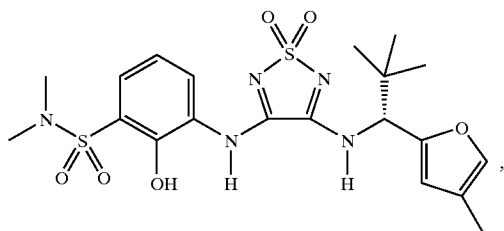
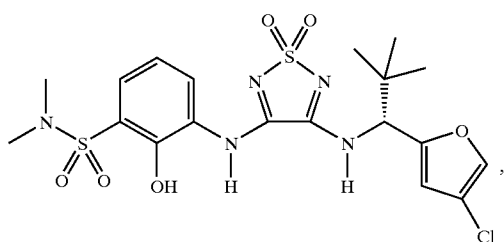
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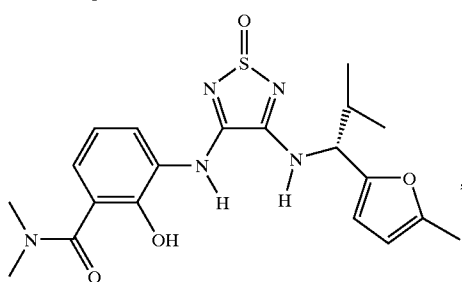
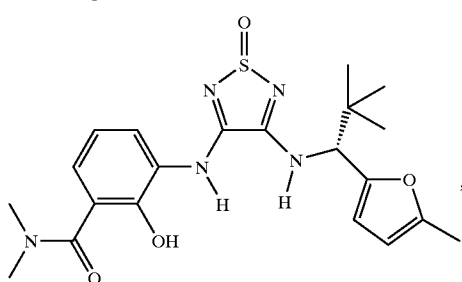
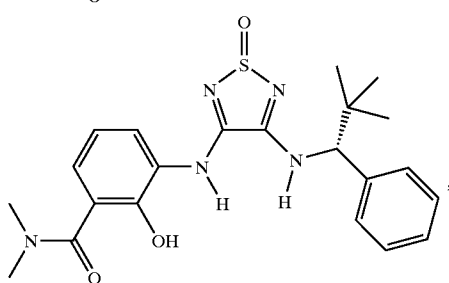
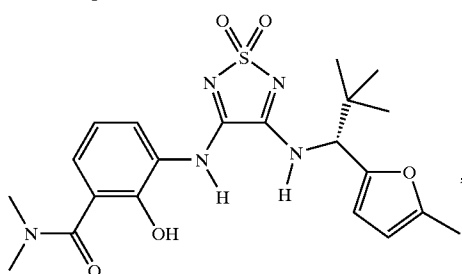
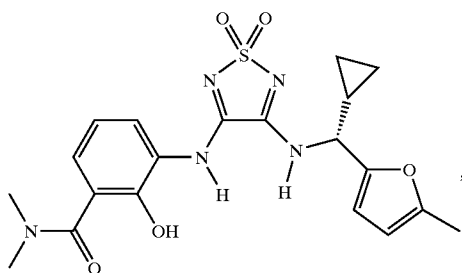
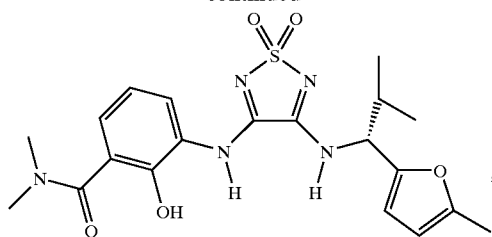
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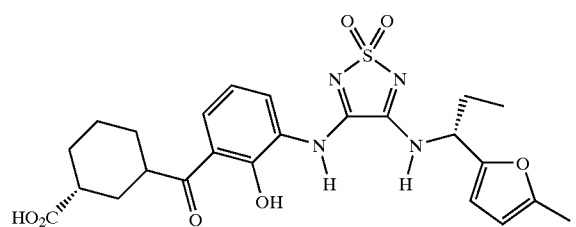
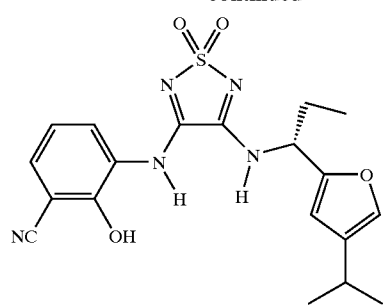
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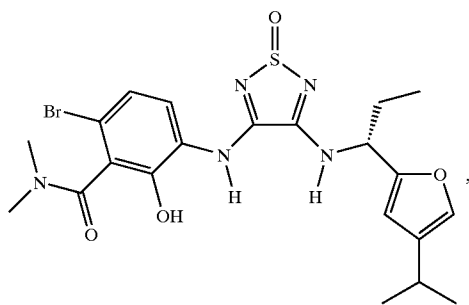
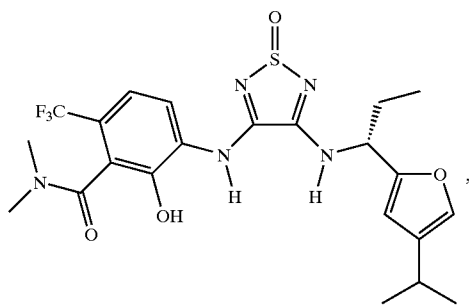
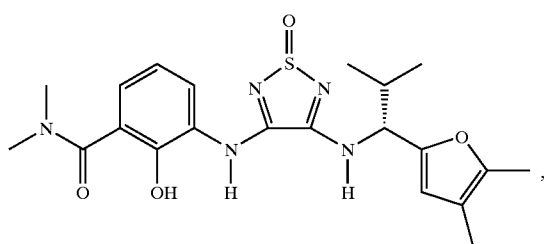
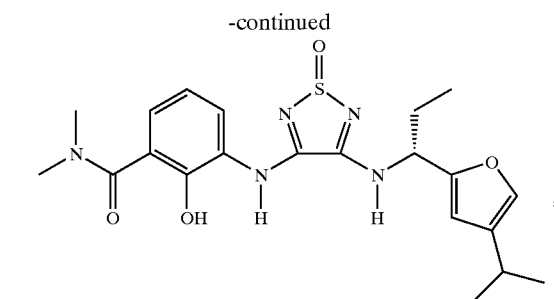
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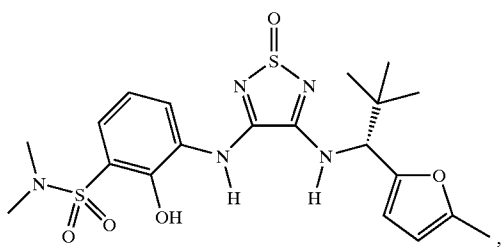
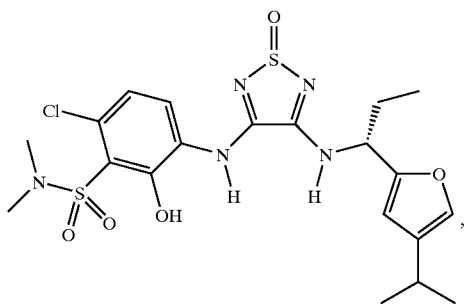
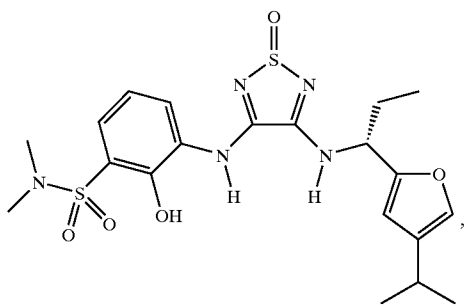
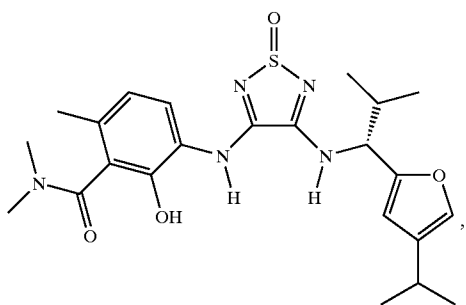
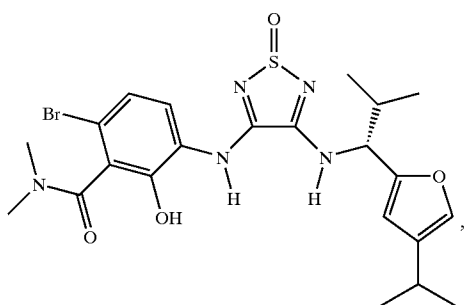
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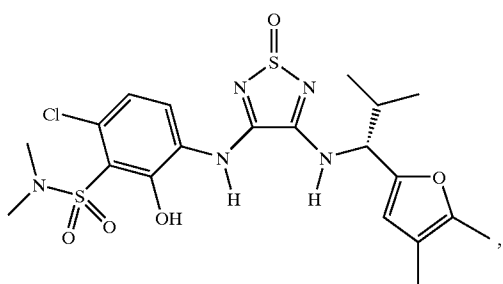
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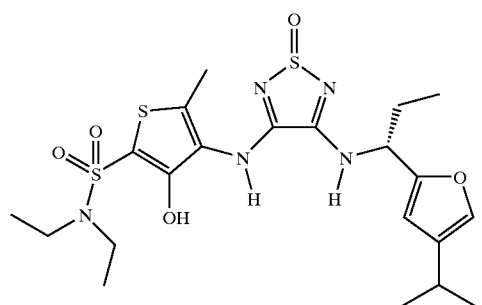
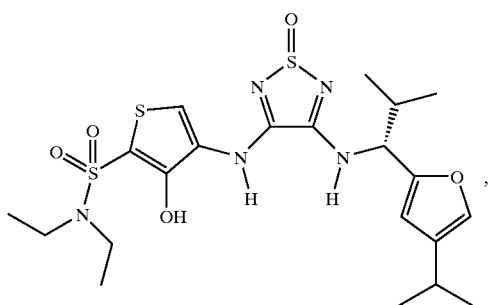
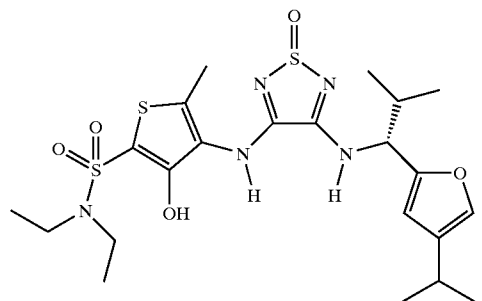
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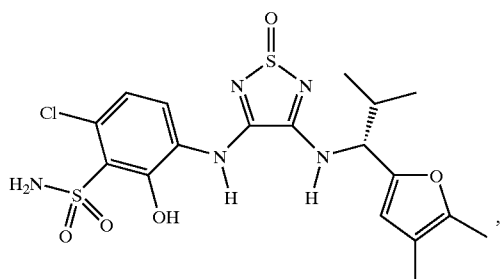
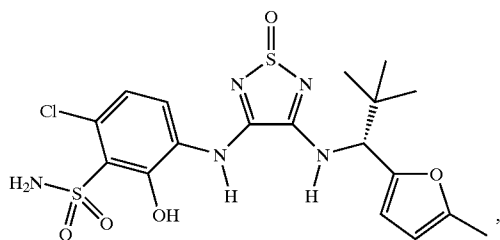
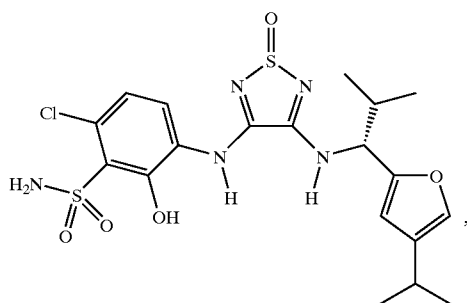
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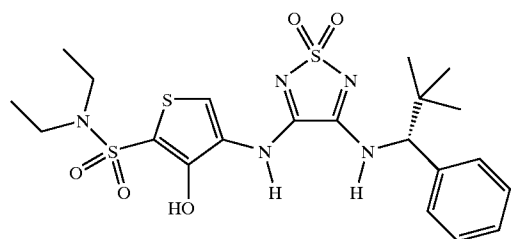
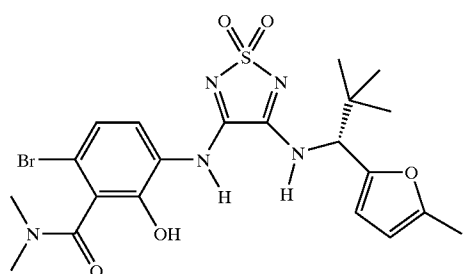
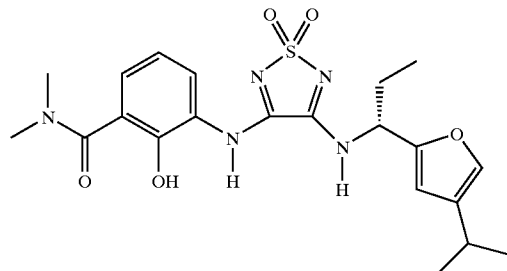
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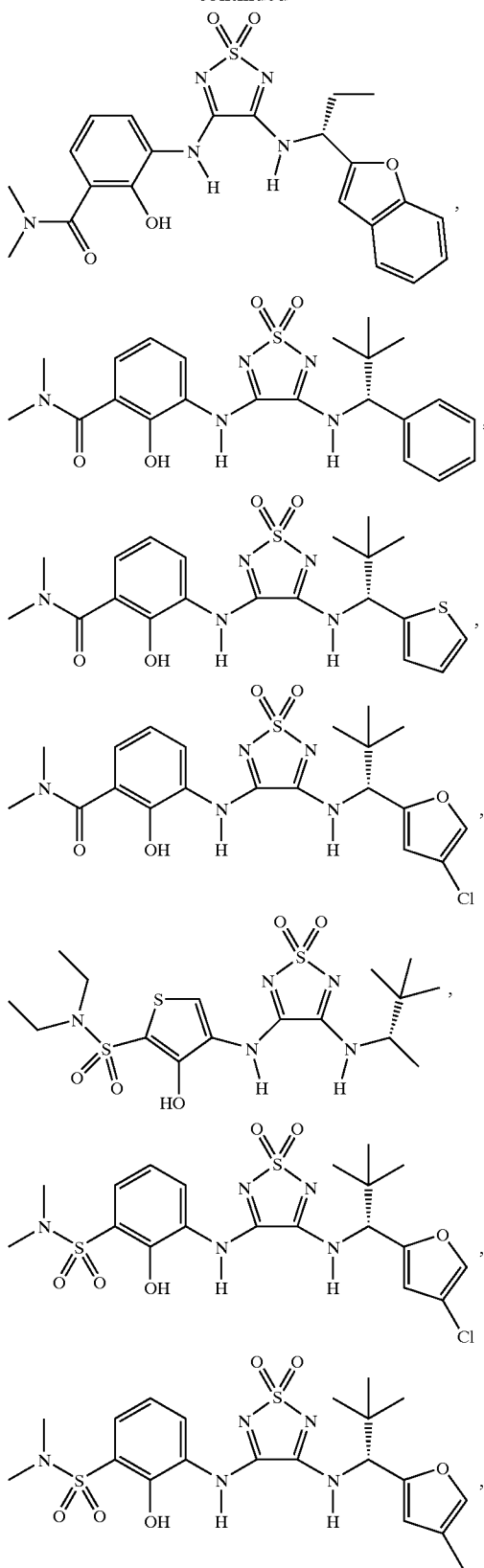


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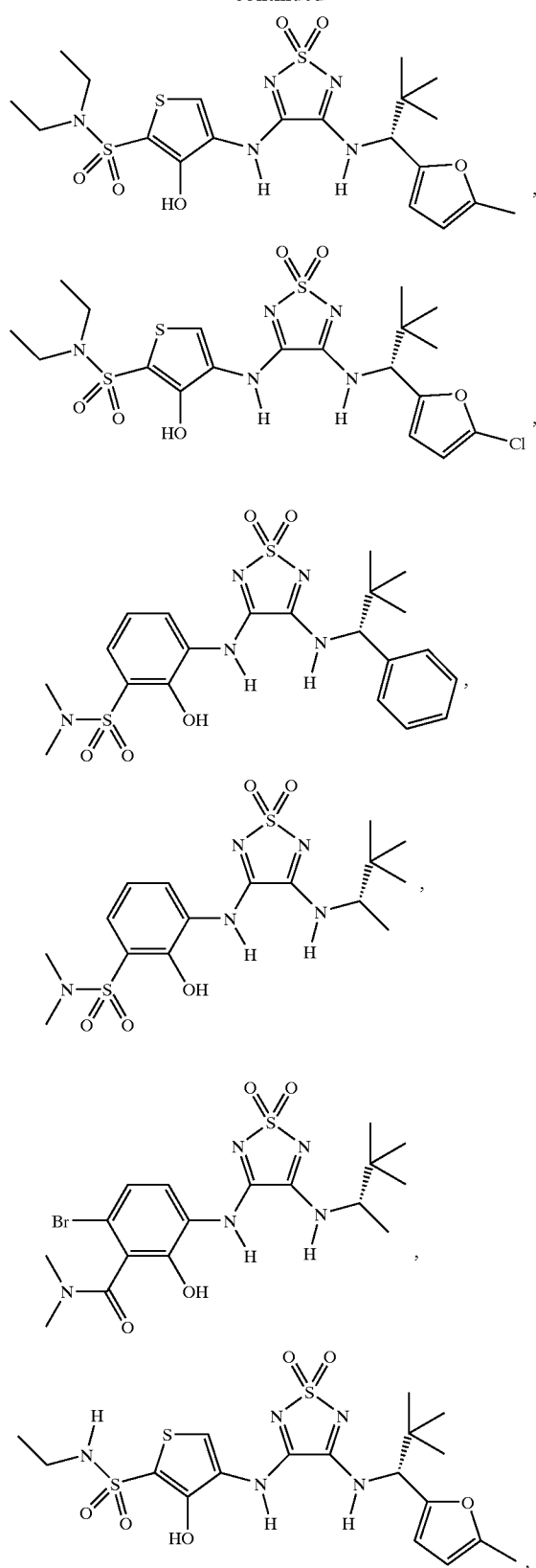


[0509] the pharmaceutically acceptable salts thereof, and the pharmaceutically acceptable

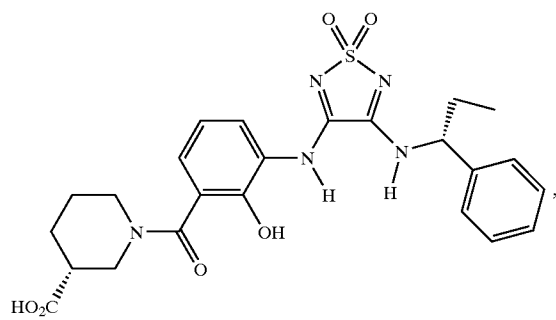
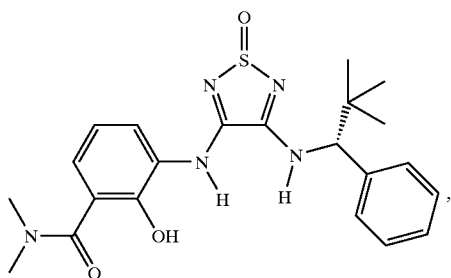
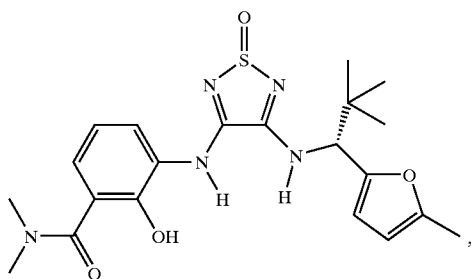
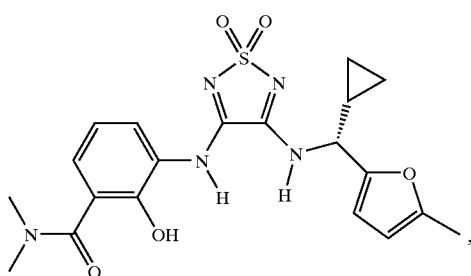
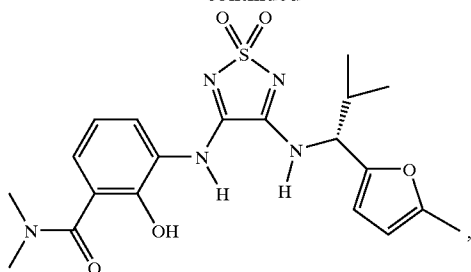
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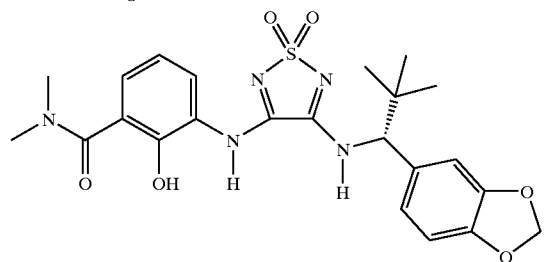
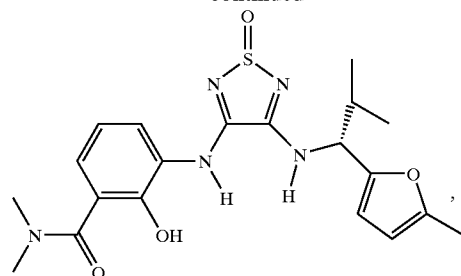
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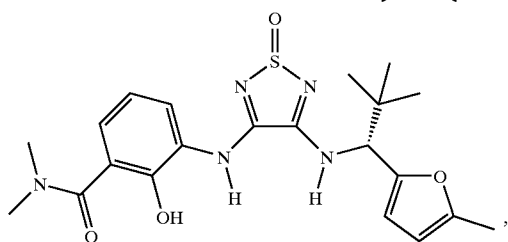
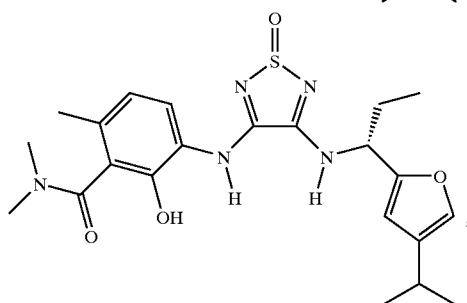
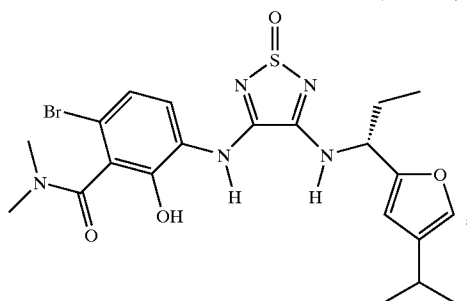
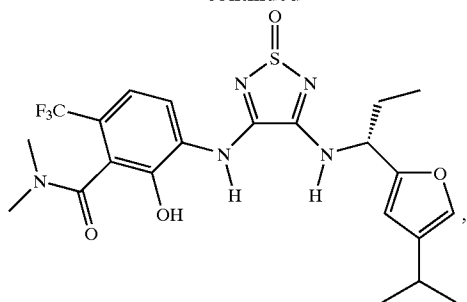
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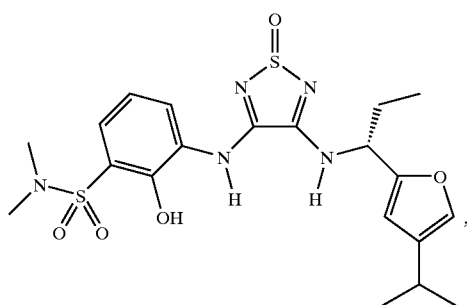
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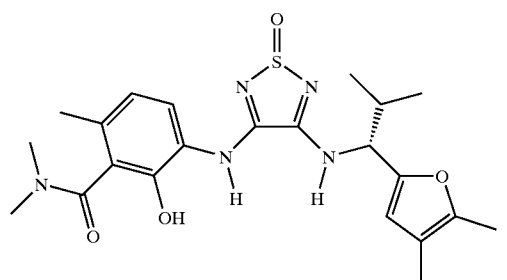
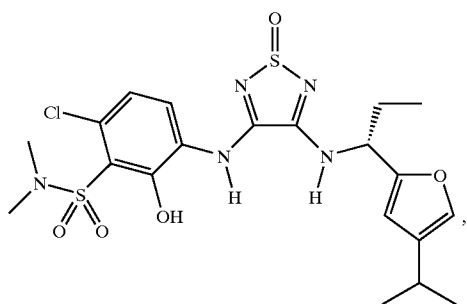
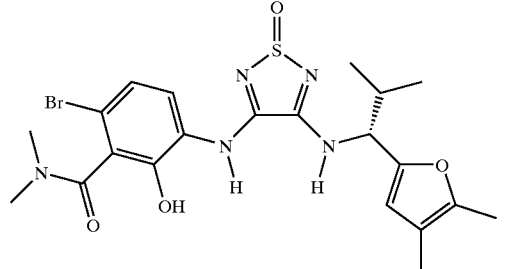
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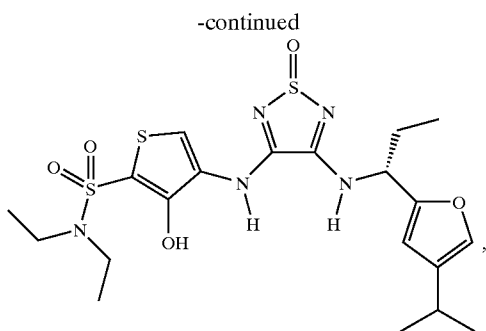
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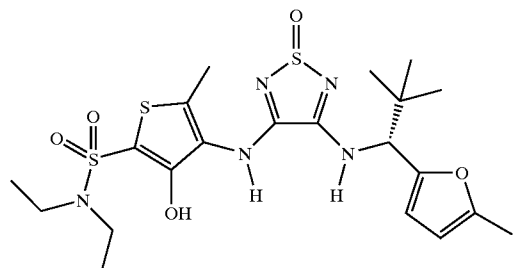
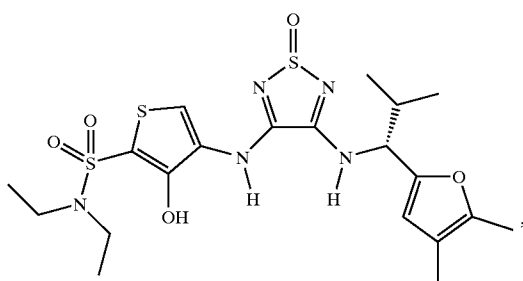
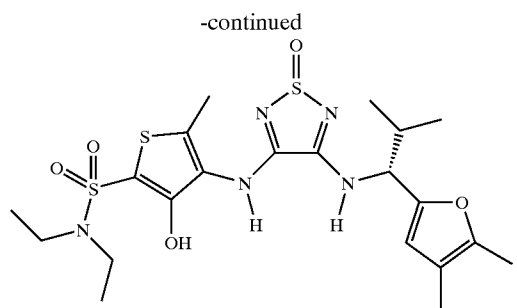
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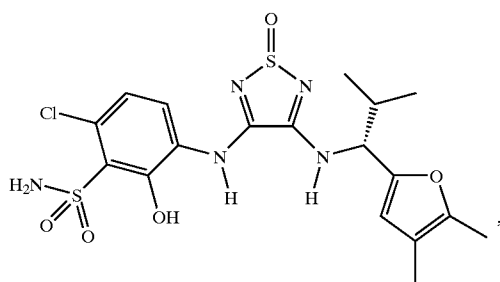
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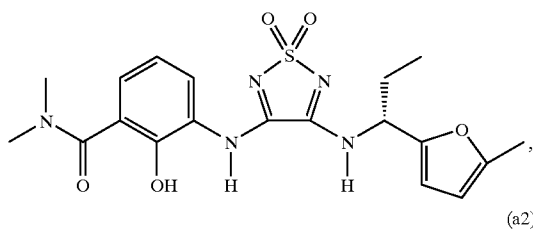
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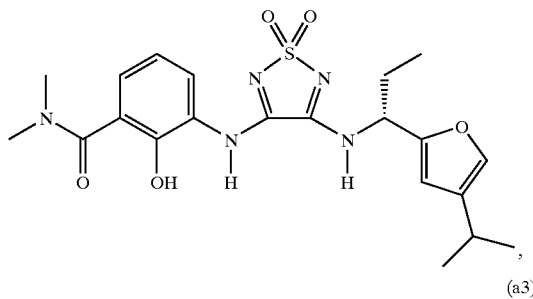
[0511] the pharmaceutically acceptable salts thereof, and the pharmaceutically acceptable solvates thereof.

[0512] Most preferred compounds of this invention are selected from the group consisting of:

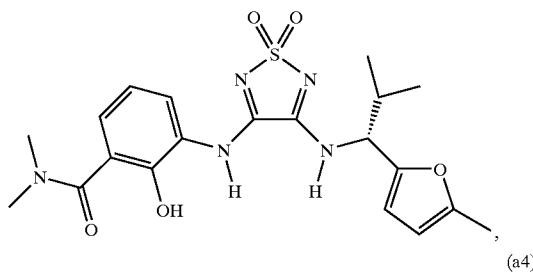
(a1)



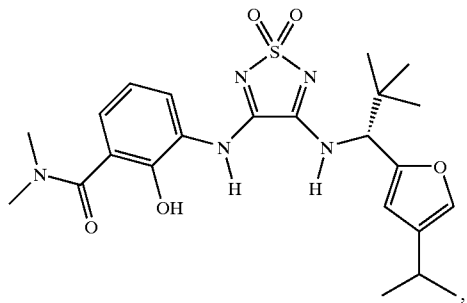
(a2)



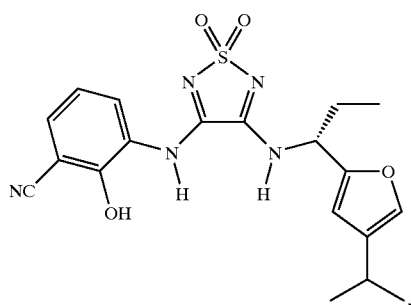
(a3)



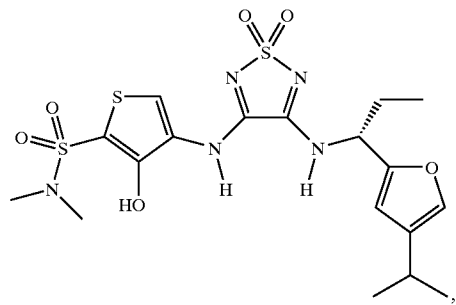
(a4)



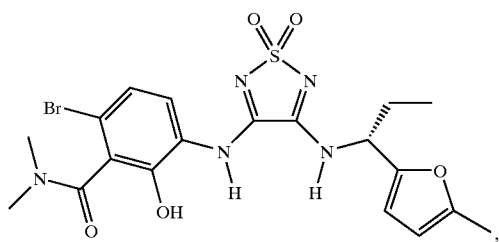
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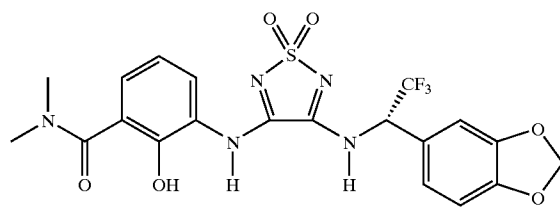
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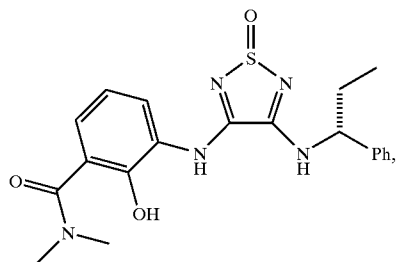
(a11)



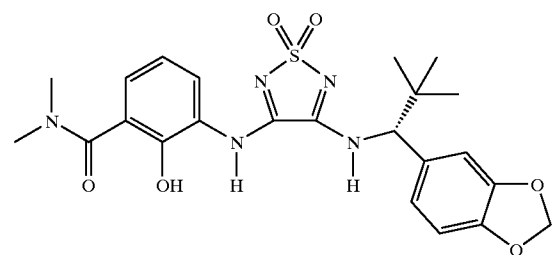
(a16)



(a12)

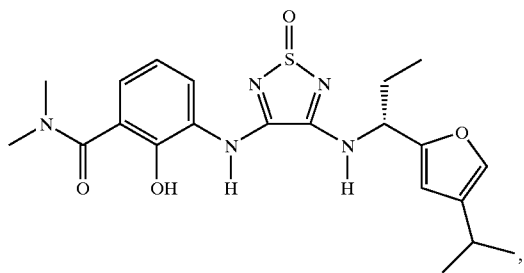


(a17)

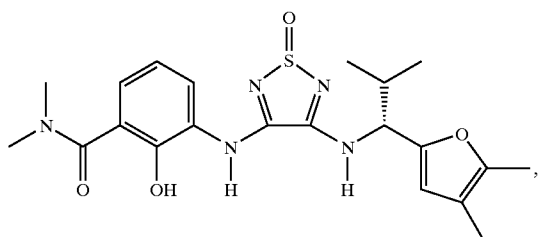


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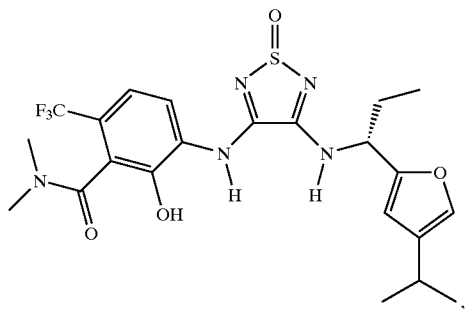
(a20)



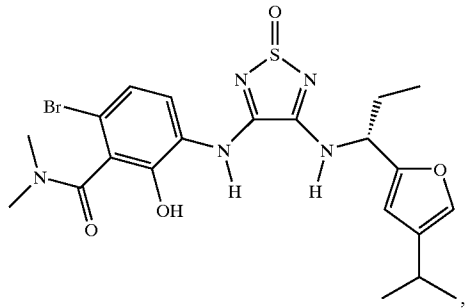
(a21)



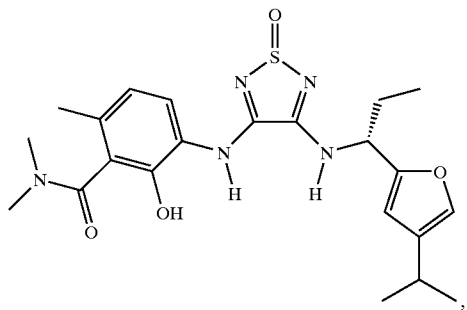
(a22)



(a23)

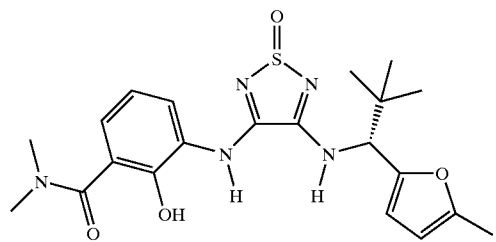


(a24)

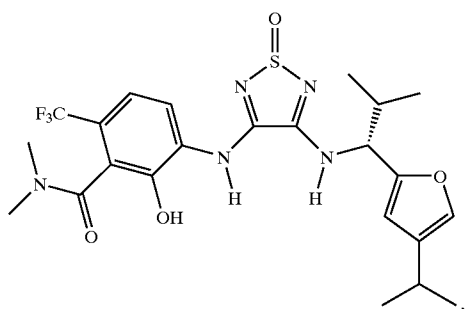


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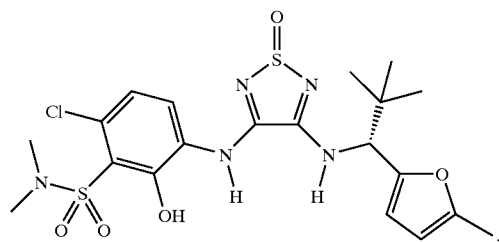
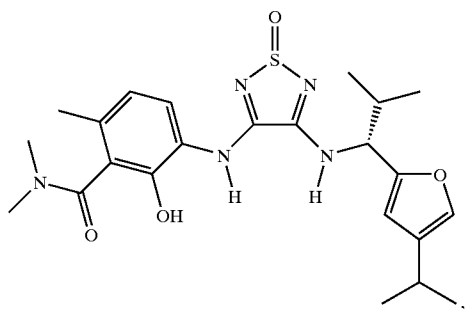
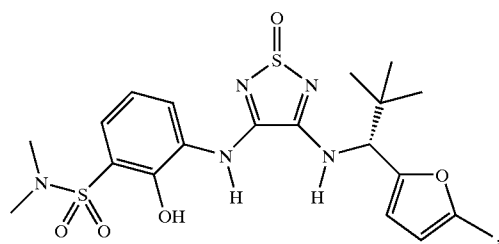
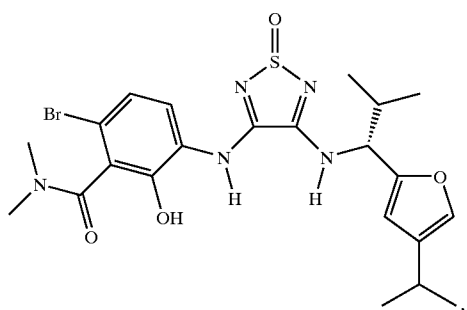
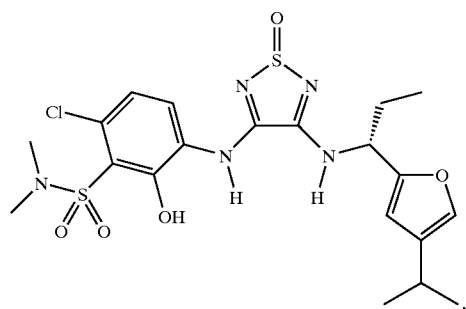
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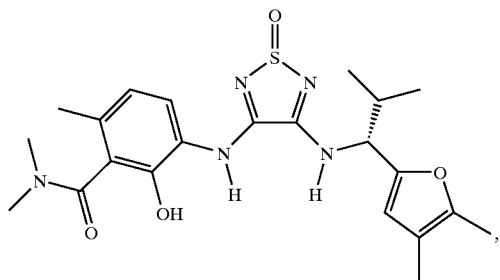


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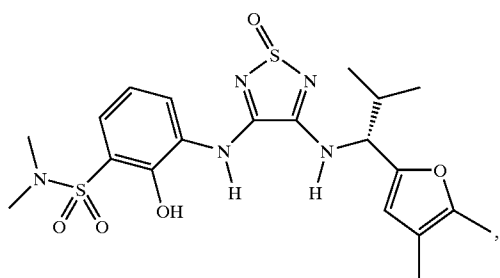


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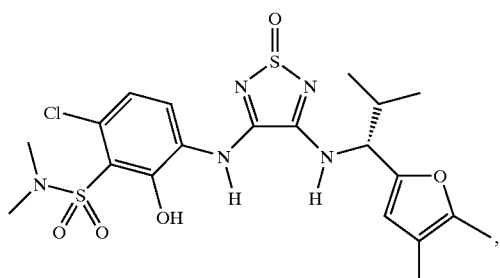
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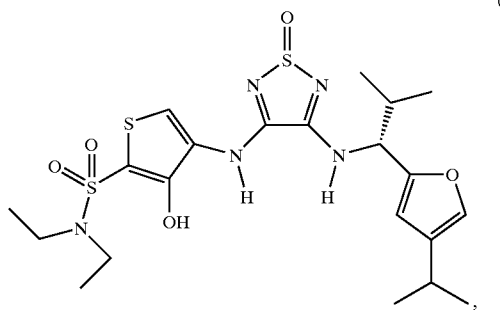
(a40)



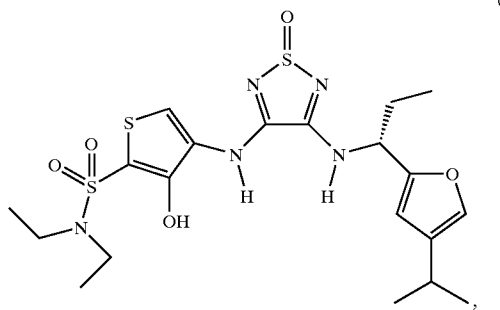
(a41)



(a42)

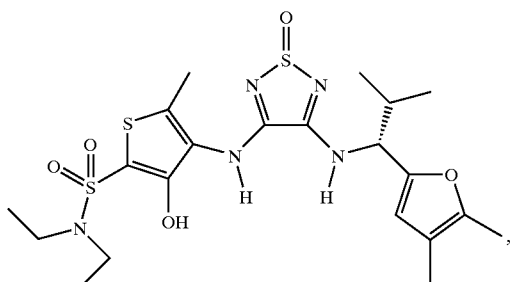


(a43)

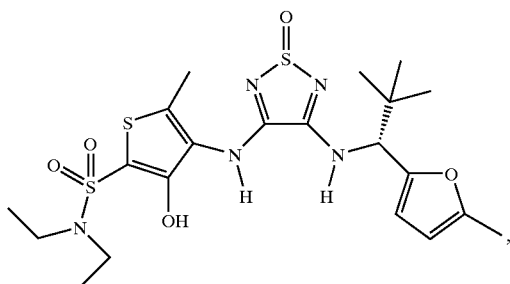


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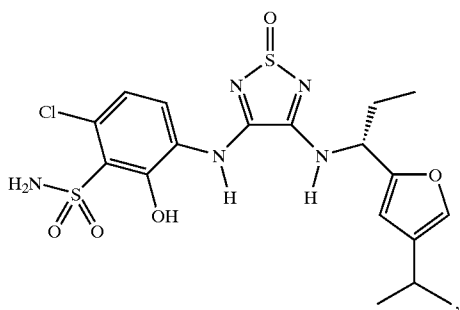
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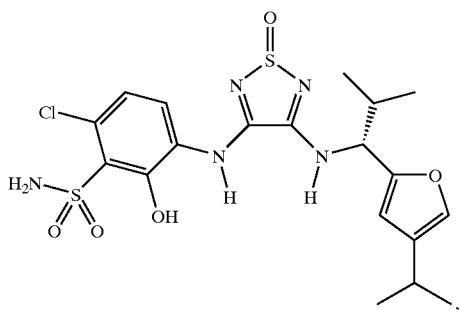
(a48)



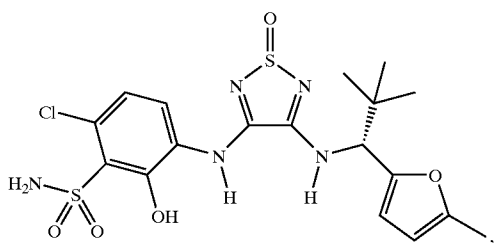
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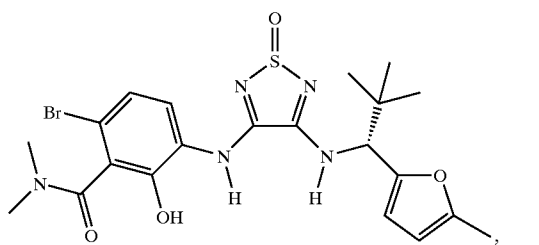
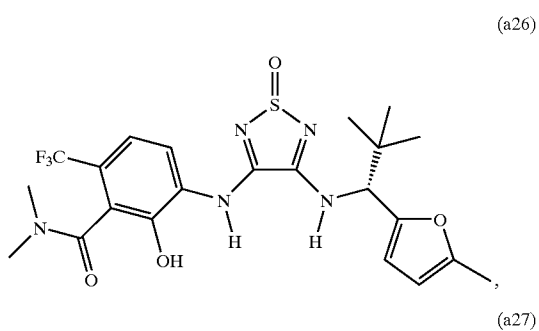
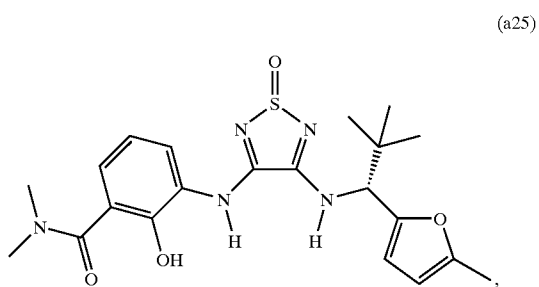
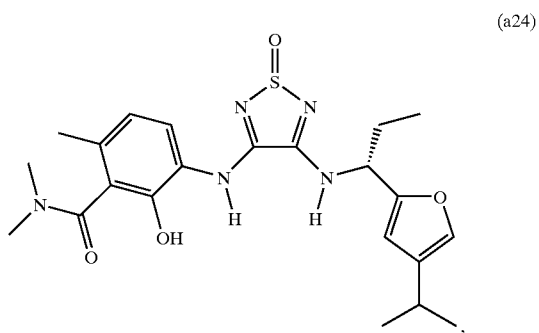
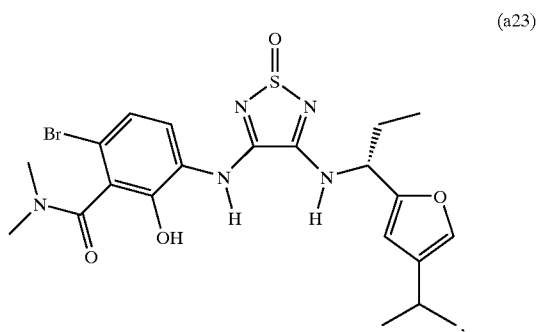
(a50)



(a51)

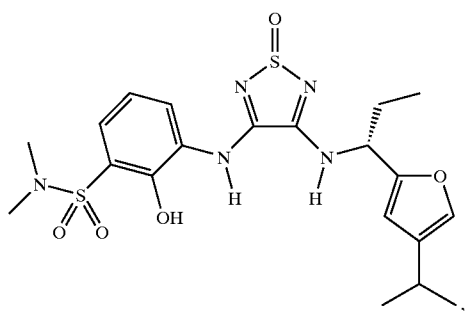


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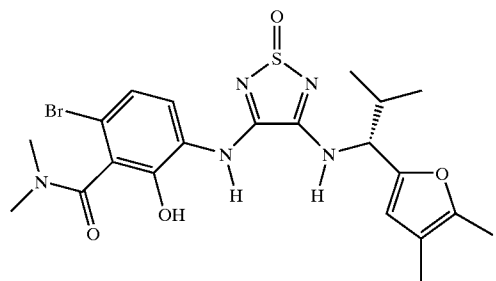
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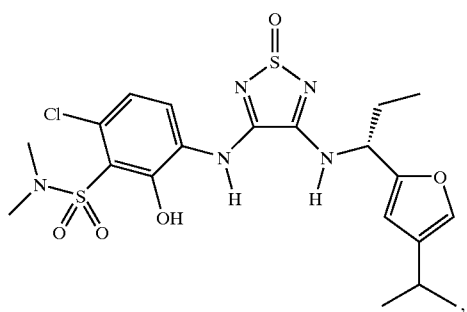


(a33)

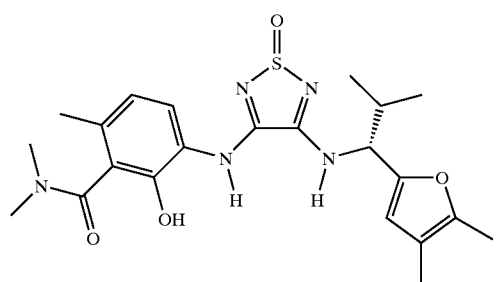
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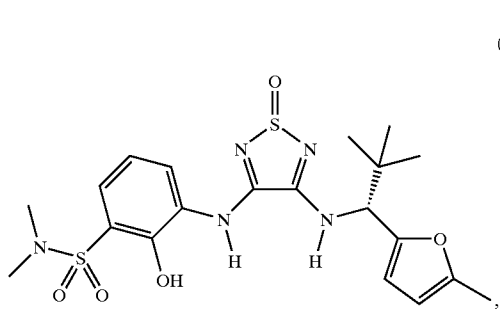
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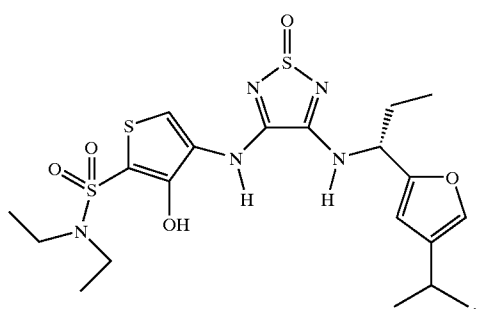
(a34)



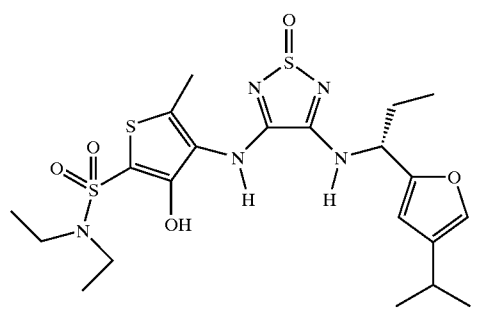
(a39)



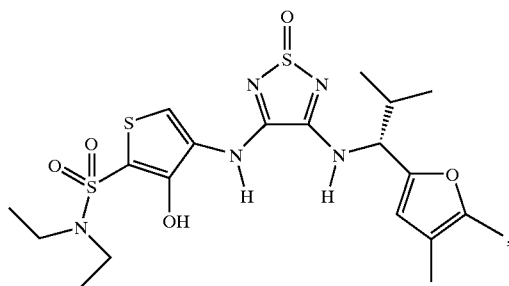
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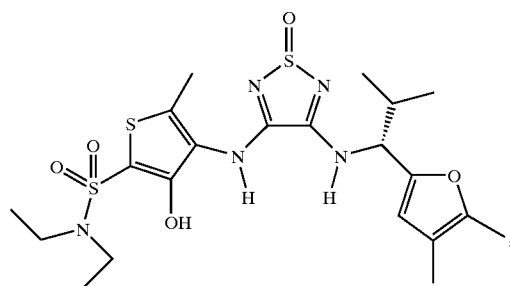
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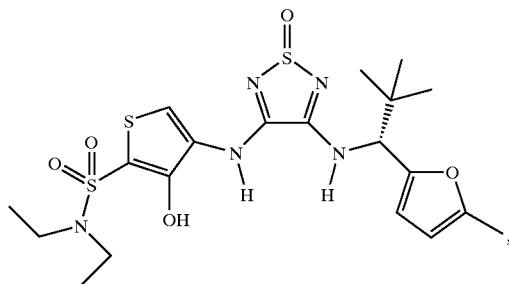
(a43)



(a47)



(a44)

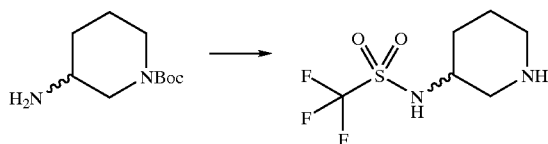


(a48)

Prep Ex.	Amine	Isocyanate	Amine
2.2			
2.3			
2.4			
2.5			
2.6			

PREPARATIVE EXAMPLE 2.7

[0616]



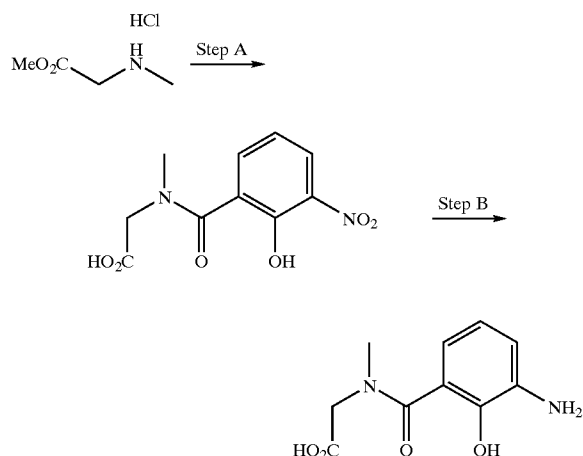
[0617] To N—BOC-3-(amino)piperidine (5 mmol) dissolved in CH_2Cl_2 (30 mL) was added trifluoromethanesulfonic anhydride (5 mmol) and the mixture was stirred overnight. The mixture was concentrated in vacuo, diluted with CH_2Cl_2 (10 mL) and treated with trifluoroacetic acid (10 mL). After stirring for 2 hr, the mixture was concentrated in vacuo to give the title compound (43%, $\text{MH}^+ = 233.1$).

PREPARATIVE EXAMPLE 2.8

[0618]

PREPARATIVE EXAMPLE 2.14

[0656]



[0657] Step A

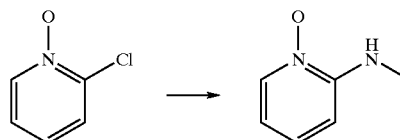
[0658] Following a similar procedure as in Preparative Example 2.13, Step A except using methyl N-methylglycinate, the desired product was obtained (18%).

[0659] Step B

[0660] Following a similar procedure as in Preparative Example 2, Step B, but using the product from Step A above, the title compound was obtained (95%, MH+=225).

PREPARATIVE EXAMPLE 2.16

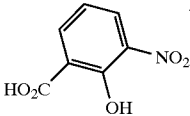
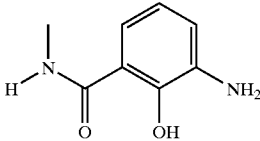
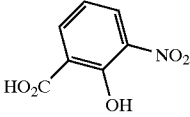
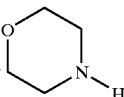
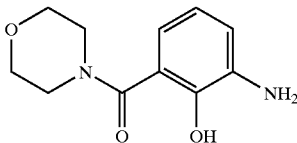
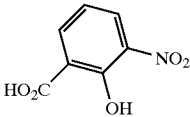
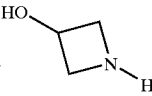
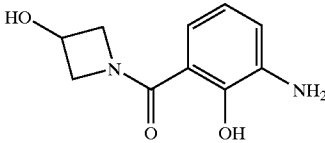
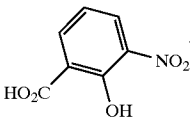
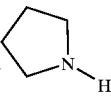
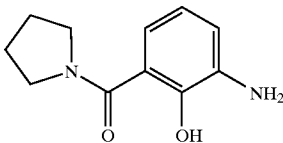
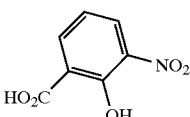
[0661]



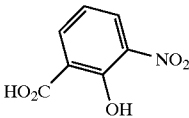

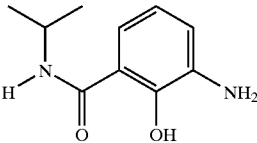
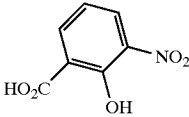

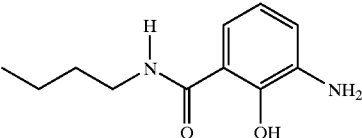
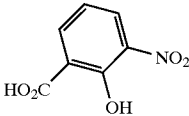
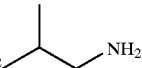
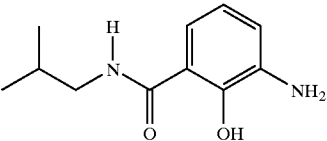
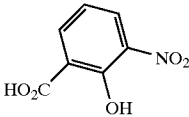
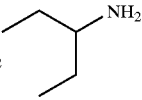
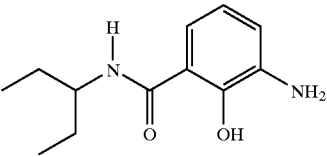
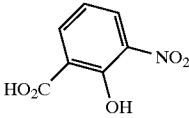
[0662] The above n-oxide (2 g) was combined with H₂NMe/H₂O (15 cm³) and heated to 140° C. overnight. Potassium carbonate (1.3 g) added and the mixture concentrated in vacuo. Extraction with EtOH and concentration of the filtrate in vacuo gave 1.56 g of crude amine (MH+=125).

PREPARATIVE EXAMPLE 3-10.50

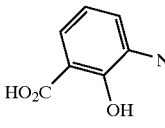
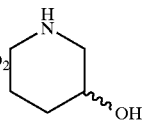
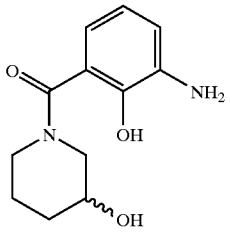
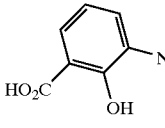
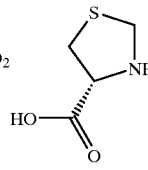
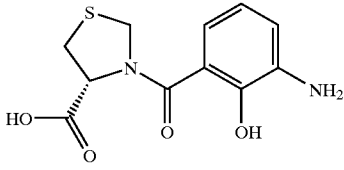
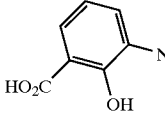
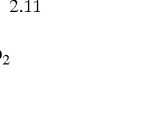
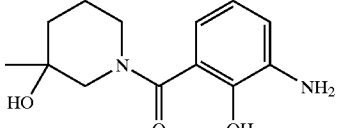
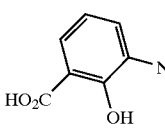

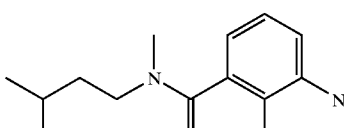
-continued

Prep Ex.	Carboxylic acid	Amine	Product 1. Coupling Agent 2. % yield 3. MH ⁺
6		—NH_2	 1. PyBroP 2. 83 3. 167
7			 1. PyBroP 2. 76 3. 223
8			 1. PyBroP 2. 65, 53 3. 209
9			 1. PyBroP 2. 59, 69 3. 207
10			

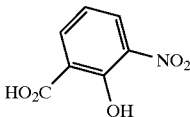
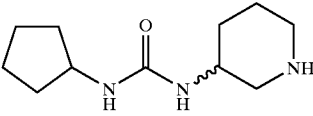
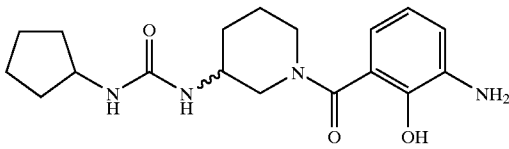
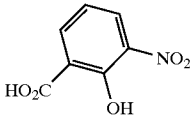
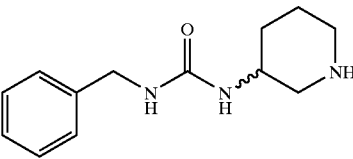
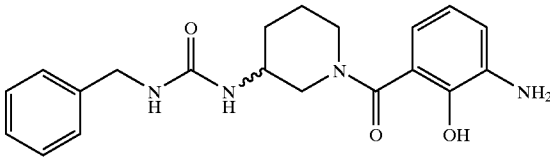
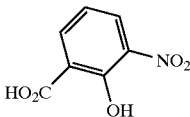
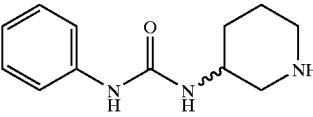
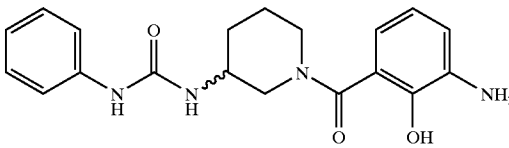
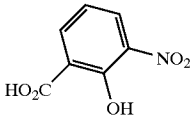
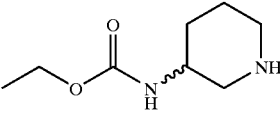
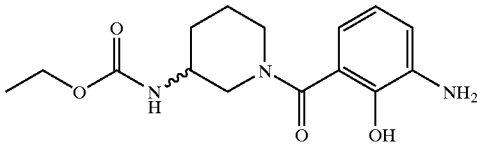
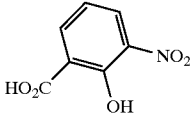
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Prep			Product
Ex.	Carboxylic acid	Amine	1. Coupling Agent 2. % yield 3. MH ⁺
10.2			1. PyBroP 2. 30, 88 3. 193 
10.3			1. PyBroP 2. 26, 87 3. 195 
10.4			1. PyBroP 2. 38 3. 209 
10.5			1. PyBroP 2. 29 3. 209 
10.6			

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Prep Ex.	Carboxylic acid	Amine	Product 1. Coupling Agent 2. % yield 3. MH ⁺
10.7			 1. PyBroP 2. 35, 99 3. 237
10.8			 1. DCC 2. 30, 99 3. 269
10.9			 1. PyBroP 2. 58, 95 3. 233.1
10.10			

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Prep Ex.	Carboxylic acid	Amine	Product 1. Coupling Agent 2. % yield 3. MH ⁺
10.14		2.2 	 1. PyBroP 2. 55 3. 347
10.15		2.1 	 1. PyBroP 2. 41 3. 369.1
10.16		2.3 	 1. PyBroP 2. 56 3. 354.9
10.17		2.5 	 1. PyBroP 2. 56 3. 308
10.18		12.4 	

