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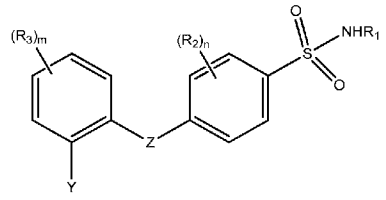

(I)

(57) Abstract: Provided herein are sodium channel modulating Compounds, in particular NaVl.7 modulating compounds of Formula I: In particular, provided herein are processes for the preparation of, intermediates used in the preparation of, pharmaceutical compositions comprising, and therapeutic methods comprising administering such compounds. In particular, provided herein are compounds for the treatment of pain.

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SODIUM CHANNEL MODULATORS FOR THE TREATMENT OF PAIN

[0001] This application claims the benefit of U.S. provisional application No. 61/787,618 filed March 15, 2013, which is incorporated by reference herein in its entirety.

1 FIELD

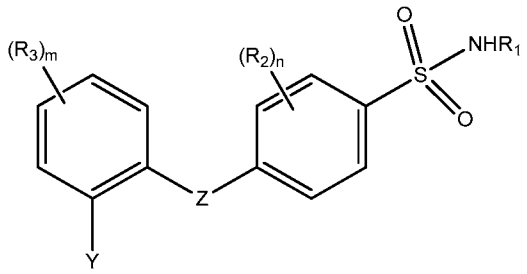
[0002] Provided herein are sodium channel modulating compounds, in particular NaV1.7 modulating compounds. In particular, provided herein are processes for the preparation of, intermediates used in the preparation of, pharmaceutical compositions comprising, and therapeutic methods comprising administering compounds. In particular, provided herein are compounds for the treatment of pain.

2 BACKGROUND

[0003] Voltage-gated ion channels play a critical role in the electrical activity of neuronal and muscle cells. Large families of voltage-gated ion channels (*e.g.*, sodium channels) have been identified. These ion channels have been the target of significant pharmacologic study, due to their potential role in a variety of pathological conditions. Biophysical and pharmacological studies have identified the sodium channel isoforms NaV1.3, NaV1.7, NaV1.8, and NaV1.9 as particularly important in the pathophysiology of pain, in particular neuropathic pain. Recently, gain-of-function mutations in SCN9A, the gene which encodes NaV1.7, have been linked to two human-inherited pain syndromes, inherited erythromelalgia and paroxysmal extreme pain disorder, while loss-of-function mutations in SCN9A have been linked to complete insensitivity to pain. Dib-Hajj *et al*, *Pain Medicine* 10(7):1260-1269 (2009) (abstract). Pain conditions affect approximately 100 million U.S. adults at a cost of $560-635 billion annually in direct medical treatment costs and lost productivity. Relieving Pain in America, *National Academies Press*, Washington, DC (2011), page 2. Unfortunately, current treatment options typically provide only partial pain relief, and are limited by inconvenient dosing and by side effects, such as somnolence, ataxia, edema, gastrointestinal discomfort and respiratory depression. Therefore, novel compounds are desirable to address the shortcomings of presently available treatment options.

3 SUMMARY

[0004] Provided herein are compounds of Formula (I),



Formula (I)

or a pharmaceutically acceptable salt, or a stereoisomeric or tautomeric form thereof, wherein:

Z is -O- or -S-;

Y is –X-C(=O)NR_4R_5, –$(CH_2)_3$-NR_9R_{10}, or 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-(2-yl or 3-yl);

X is (C_6-C_{10})aryl or 5- or 6-membered heteroaryl;

R_1 is a partially unsaturated or aromatic 5- or 6-membered heterocycle;

R_2 is independently at each occurrence –F, -Cl, -Br, -CH_3 or -CN;

R_3 is independently at each occurrence –H, -F, -Cl, -Br, -CF_3, -OCF_3, -CN, (C_1-C_{12})alkyl, or (C_1-C_{12})alkoxy;

R_4 and R_5 are each independently H, (C_1-C_9)alkyl, (C_4-C_{12})cycloalkyl, or R_4 and R_5 together form a 5- to 7-membered heterocycloalkyl ring; with the proviso that:

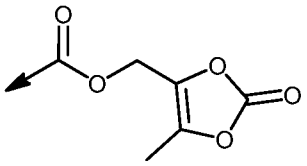
R_4 and R_5 are not both H; and

at least one of R_4 and R_5 independently or said heterocycloalkyl ring formed by R_4 and R_5 together is substituted with 1 or 2 substituents selected from the group consisting of –CO_2H, -CO_2R_6, -CN, -OH, -$CONR_7R_8$, and -NR_7R_8; wherein:

R_6 is (C_1-C_{12})alkyl;

R_7 and R_8 are each independently H, (C_1-C_{12})alkyl, or R_7 and R_8 together form a 4- to 7-membered heterocycloalkyl ring;

R_9 is (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, pyrazolyl or pyridinyl; wherein R_9 is optionally further substituted with 1 or 2 substituents selected from the group consisting of -COOH, -$COOR_{11}$, -$CONR_{11}R_{12}$, -SO_2R_{11}, -$SO_2NR_{11}R_{12}$, -OH, -CN, -OR_{11}, and -$NR_{11}R_{12}$; wherein R_{11} and R_{12} may form a 6 membered heterocycloalkyl ring



R_{10} is R_{11}, $-COR_{11}$, $-COOR_{11}$, $-SO_2R_{11}$, 5-methyl-2-oxo-1,3-dioxol-4-yl, , $-COO-CH(CH_3)OCOCH(CH_3)_2$; or R_9 and R_{10} together form a piperazinone or a 4-to 8-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is substituted with 1 or 2 substituents selected from the group consisting of –COOH, $-COOR_{11}$, $-CH_2-COOR_{11}$, -OH, $-NH_2$, -CN, and (C_1-C_8)alkoxy;

R_{11} and R_{12} are independently H or (C_1-C_6)alkyl, optionally substituted with 4- to 8-membered heterocycloalkyl ring; and

m and n are each independently 1, 2, 3, or 4.

[0005] In a certain embodiment, the compounds of Formula (I) are those wherein Y is $-(CH_2)_3-NR_9R_{10}$.

[0006] In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is an aromatic 5- or 6-membered heterocycle, with 1-3 heteroatoms independently selected from the group consisting of N, O, and S.

[0007] In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is pyridyl or pyrimidinyl.

[0008] In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is an aromatic 5-membered heterocycle with 1 or 2 nitrogen atoms and optionally 1 or 2 sulphur atoms. In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is thiazolyl, isothiazolyl, or thiadiazolyl. In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is thiazolyl. In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is 1,2,4-thiadiazol-5-yl.

[0009] In a particular embodiment, the compounds of Formula (I) are those wherein R_2 is independently at each occurrence –F or -Cl.

[0010] In a particular embodiment, the compounds of Formula (I) are those wherein n is 1, 2, or 3. In a particular embodiment, the compounds of Formula (I) are those wherein n is 2.

[0011] In a particular embodiment, the compounds of Formula (I) are those wherein Z is –O-.

[0012] In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is independently at each occurrence -H, –F, -Cl, or -Br. In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is –H or –Cl. In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is –Cl.

[0013] In a particular embodiment, the compounds of Formula (I) are those wherein m is 1, 2, or 3. In a particular embodiment, the compounds of Formula (I) are those wherein m is 1.

[0014] In a particular embodiment, the compounds of Formula (I) are those wherein R_9 is $(C_1\text{-}C_6)$alkyl; wherein R_9 is optionally further substituted with 1 or 2 substituents selected from the group consisting of -COOH, -COOMe, $-CONH_2$, and $–NH_2$. In a particular embodiment, the compounds of Formula (I) are those wherein R_9 is methyl or ethyl. In a particular embodiment, the compounds of Formula (I) are those wherein R_9 is further substituted with -COOH.

[0015] In a particular embodiment, the compounds of Formula (I) are those wherein R_{10} is –H, –COMe, -COOEt. In a particular embodiment, the compounds of Formula (I) are those wherein R_{10} is -H or –COMe. In a particular embodiment, the compounds of Formula (I) are those wherein R_{10} is -H.

[0016] In a particular embodiment, the compounds of Formula (I) are those wherein R_9 and R_{10} together form a 4 to 8 membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is substituted with 1 or 2 groups selected from the group consisting of -COOH, –COOMe, –COOEt, $-CH_2$-COOH, and $-NH_2$. In a particular embodiment, the compounds of Formula (I) are those wherein R_9 and R_{10} together form a 4 to 8 membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is substituted with 1 or 2 groups selected from the group consisting of –COOH, $-CH_2$-COOH, and $-NH_2$.

[0017] In a particular embodiment, the compounds of Formula (I) are those wherein R_9 and R_{10} together form a piperidine substituted with 1 or 2 groups selected from the group consisting of –COOH, –COOMe, –COOEt, $-CH_2$-COOH, $-CH_2$-COOMe, $-CH_2$-COOEt, and $-NH_2$. In a particular embodiment, the compounds of Formula (I) are those wherein R_9 and

R_{10} together form a piperidine substituted with 1 or 2 groups selected from the group consisting of –COOH, -CH_2-COOH, and -NH_2.

[0018] In a certain embodiment, the compounds of Formula (I) are those wherein Y is -X-C(=O)NR_4R_5.

[0019] In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is an aromatic 5- or 6-membered heterocycle, with 1-3 heteroatoms independently selected from the group consisting of N, O, and S.

[0020] In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is pyridyl or pyrimidinyl.

[0021] In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is an aromatic 5-membered heterocycle with 1 or 2 nitrogen atoms and optionally 1 or 2 sulphur atoms. In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is thiazolyl, isothiazolyl, or thiadiazolyl. In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is thiazolyl. In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is 1,2,4-thiadiazol-5-yl.

[0022] In a particular embodiment, the compounds of Formula (I) are those wherein R_2 is independently at each occurrence -F or -Cl.

[0023] In a particular embodiment, the compounds of Formula (I) are those wherein n is 1, 2, or 3. In a particular embodiment, the compounds of Formula (I) are those wherein n is 2.

[0024] In a particular embodiment, the compounds of Formula (I) are those wherein Z is –O-.

[0025] In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is independently at each occurrence -F, -Cl, or -Br. In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is –H or –Cl. In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is –Cl.

[0026] In a particular embodiment, the compounds of Formula (I) are those wherein m is 1, 2, or 3. In a particular embodiment, the compounds of Formula (I) are those wherein m is 1.

[0027] In a particular embodiment, the compounds of Formula (I) are those wherein X is 5- or 6-membered heteroaryl. In a particular embodiment, the compounds of Formula (I) are those wherein X is pyridyl or pyrimidinyl. In a particular embodiment, the compounds of Formula (I) are those wherein X is pyridyl.

[0028] In a particular embodiment, the compounds of Formula (I) are those wherein R_4 is H and R_5 is $(C_1\text{-}C_9)$alkyl.

[0029] In a particular embodiment, the compounds of Formula (I) are those wherein R_5 is methyl or ethyl, substituted with 1 or 2 substituents selected from the group consisting of $-CO_2H$, $-CO_2R_6$, and $-CONR_7R_8$.

[0030] In a particular embodiment, the compounds of Formula (I) are those wherein R_6 is $(C_1\text{-}C_6)$alkyl.

[0031] In a particular embodiment, the compounds of Formula (I) are those wherein R_5 is methyl or ethyl, substituted with $-CO_2H$.

[0032] In a certain embodiment, the compounds of Formula (I) are those wherein Y is 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-(2-yl or 3-yl). In a particular embodiment, the compounds of Formula (I) are those wherein Y is 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-yl.

[0033] In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is an aromatic 5- or 6-membered heterocycle, with 1-3 heteroatoms independently selected from the group consisting of N, O, and S.

[0034] In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is pyridyl or pyrimidinyl.

[0035] In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is an aromatic 5-membered heterocycle with 1 or 2 nitrogen atoms and optionally 1 or 2 sulphur

atoms. In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is thiazolyl, isothiazolyl, or thiadiazolyl. In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is thiazolyl. In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is 1,2,4-thiadiazol-5-yl.

[0036] In a particular embodiment, the compounds of Formula (I) are those wherein R_2 is independently at each occurrence -F or -Cl.

[0037] In a particular embodiment, the compounds of Formula (I) are those wherein n is 1, 2, or 3. In a particular embodiment, the compounds of Formula (I) are those wherein n is 2.

[0038] In a particular embodiment, the compounds of Formula (I) are those wherein Z is –O-.

[0039] In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is independently at each occurrence -F, -Cl, or -Br. In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is –H or –Cl. In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is –Cl.

[0040] In a particular embodiment, the compounds of Formula (I) are those wherein m is 1, 2, or 3. In a particular embodiment, the compounds of Formula (I) are those wherein m is 1.

[0041] In a certain embodiment, the compounds of Formula (I) are those wherein the compound is
3-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid,
2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)acetic acid,
5-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)pentanoic acid,
4-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)butanoic acid,
2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid,

(R)-2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid,
2-(6-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)acetic acid,
(S)-2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid,
3-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-cyanophenoxy)-5-chlorophenyl)picolinamido)propanoic acid,
3-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2,5-difluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid,
2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid,
3-((3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)amino)propanoic acid,
2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid,
1-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)piperidine-4-carboxylic acid,
3-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid,
4-amino-1-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)piperidine-4-carboxylic acid,
2-amino-4-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)butanoic acid,
2-((3-(5-chloro-2-(2,5-difluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid,
1-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)piperidine-3-carboxylic acid,
2-((3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)phenyl)propyl)amino)acetic acid,
2-((3-(5-chloro-2-(2,5-difluoro-4-(N-(thiazol-4-

yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid,
3-((3-(5-chloro-2-(2,5-difluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid,
3-((3-(5-chloro-2-(2-cyano-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid,
methyl 2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetate,
3-((3-(2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)-5-fluorophenyl)propyl)amino)propanoic acid,
3-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanamide,
2-(N-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)acetamido)acetic acid,
2-(1-(3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)piperidin-4-yl)acetic acid,
3-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid,
2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)-N-methylacetamide,
5-chloro-4-(4-chloro-2-(3-((2-(methylsulfonyl)ethyl)amino)propyl)phenoxy)-2-fluoro-N-(thiazol-4-yl)benzenesulfonamide,
1-(3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)piperidine-4-carboxylic acid, or
5-chloro-4-(4-chloro-2-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl)phenoxy)-2-fluoro-N-(thiazol-4-yl)benzenesulfonamide; or a pharmaceutically acceptable salt, or a stereoisomeric or tautomeric form thereof.

[0042] In a particular embodiment, the compounds of Formula (I) are those wherein the compound is
2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)acetic acid,
3-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-

chlorophenyl)picolinamido)propanoic acid,
2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid, or
3-((3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)amino)propanoic acid; or a pharmaceutically acceptable salt, or a stereoisomeric or tautomeric form thereof.

[0043] Provided herein are methods for treating neuropathic pain comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate or tautomeric form thereof.

[0044] Provided herein are methods for treating pain comprising use of a compound of Formula (I), as a voltage-gated sodium channel inhibitor. In a particular embodiment the methods are those, wherein the pain is neuropathic, nociceptive or inflammatory pain. In a particular embodiment the methods are those, wherein the voltage-gated sodium channel is NaV1.7.

[0045] Provided herein are pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable carrier. In a particular embodiment the pharmaceutical compositions are those, wherein the composition is suitable for topical, oral, subcutaneous, or intravenous administration.

[0046] Provided herein are methods for prevention or treatment of pain in a subject, wherein the method comprises administering to the subject in need of such prevention or treatment a therapeutically effective amount of a compound of Formula (I). In a particular embodiment the methods are those, wherein the therapeutically effective amount is effective to alleviate pain in a subject, wherein the compound of Formula (I) shows a reduction in pain response in the Formalin Assay (in phase 1 or phase 2, or both) (*see* Section 5.1.2) at a dose between 0.1 mg/kg and 1,000 mg/kg, at a dose between 0.5 mg/kg and 100 mg/kg, at a dose between 1 mg/kg to 50 mg/kg, or at a dose of 5 mg/kg. In certain embodiments, a compound of Formula (I) provided herein shows a reduction in pain response in the Formalin Assay (in phase 1 or phase 2, or both) by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 98%, 99%, or 100%, or by ranges between any of the recited percentages (*e.g.*, 10-20%, 10-30%, 10-

40%, 20-30%, or 20-40%) relative to a vehicle control. In a particular embodiment the methods are those, wherein the pain is nociceptive pain, such as that resulting from physical trauma (*e.g.*, a cut or contusion of the skin; or a chemical or thermal burn), osteoarthritis, rheumatoid arthritis or tendonitis; myofascial pain; neuropathic pain, such as that associated with stroke, diabetic neuropathy, luetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, fibromyalgia, or painful neuropathy induced iatrogenically by drugs; or mixed pain (*i.e.*, pain with both nociceptive and neuropathic components); visceral pain; headache pain (*e.g.*, migraine headache pain); CRPS; CRPS type I; CRPS type II; RSD; reflex neurovascular dystrophy; reflex dystrophy; sympathetically maintained pain syndrome; causalgia; Sudeck atrophy of bone; algoneurodystrophy; shoulder hand syndrome; post-traumatic dystrophy; autonomic dysfunction; autoimmune-related pain; inflammation-related pain; cancer-related pain; phantom limb pain; chronic fatigue syndrome; post-operative pain; spinal cord injury pain; central post-stroke pain; radiculopathy; sensitivity to temperature, light touch or color change to the skin (allodynia); pain from hyperthermic or hypothermic conditions; and other painful conditions (*e.g.*, diabetic neuropathy, luetic neuropathy, postherpetic neuralgia, trigeminal neuralgia); chronic pain; or acute pain.

[0047] Provided herein are methods modulating the activity of a voltage-gated sodium channel, wherein the method comprises contacting a cell that expresses the voltage-gated sodium channel with a compound of Formula (I). In a particular embodiments the methods are those, wherein the voltage-gated sodium channel is NaV1.7. In a particular embodiments the methods are those, wherein the method results in inhibition of the voltage-gated sodium channel.

4 DETAILED DESCRIPTION

4.1 Definitions

[0048] A "Compound" or "Compounds" as used herein comprise a compound of Formula (I), a compound of Formula (Ia), a compound of Formula (Ib), a compound of Formula (Ic), a compound of Formula (Id), a compound listed in Table 1, or a compound listed in Table 2.

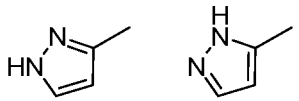
[0049] A "pharmaceutically acceptable salt(s)" refers to a salt prepared from a pharmaceutically acceptable non-toxic acid or base including an inorganic acid and base and an organic acid and base. Suitable pharmaceutically acceptable base addition salts of the

Compounds inhibitors include, but are not limited to metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Suitable non-toxic acids include, but are not limited to, inorganic and organic acids such as acetic, alginic, anthranilic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, formic, fumaric, furoic, galacturonic, gluconic, glucuronic, glutamic, glycolic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phenylacetic, phosphoric, propionic, salicylic, stearic, succinic, sulfanilic, sulfuric, tartaric acid, and p-toluenesulfonic acid. Specific non-toxic acids include hydrochloric, hydrobromic, phosphoric, sulfuric, and methanesulfonic acids. Others are well known in the art, see for example, *Remington's Pharmaceutical Sciences*, 18th eds., Mack Publishing, Easton PA (1990) or *Remington: The Science and Practice of Pharmacy*, 19th eds., Mack Publishing, Easton PA (1995).

[0050] A "stereoisomer" or "stereoisomeric form" refers to one stereoisomer of a Compound that is substantially free of other stereoisomers of that Compound. For example, a stereomerically pure compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. The Compounds can have chiral centers and can occur as racemates, individual enantiomers or diastereomers, and mixtures thereof. All such isomeric forms are included within the embodiments disclosed herein, including mixtures thereof. The use of stereomerically pure forms of such Compounds, as well as the use of mixtures of those forms, are encompassed by the embodiments disclosed herein. For example, mixtures comprising equal or unequal amounts of the enantiomers of a particular Compound may be used in methods and compositions disclosed herein. These isomers may be

asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. *See, e.g.*, Jacques, J., *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen, S. H., et al., *Tetrahedron* 33:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw Hill, NY, 1962); and Wilen, S. H., Tables of *Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

[0051] "Tautomers" refers to isomeric forms of a compound that are in equilibrium with each other. The concentrations of the isomeric forms will depend on the environment the compound is found in and may be different depending upon, for example, whether the compound is a solid or is in an organic or aqueous solution. For example, in aqueous solution, pyrazoles may exhibit the following isomeric forms, which are referred to as tautomers of each other:



[0052] As readily understood by one skilled in the art, a wide variety of functional groups and other structures may exhibit tautomerism and all tautomers of the Compounds provided herein are within the scope of the present disclosure.

[0053] An "aryl" group is an aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (*e.g.*, phenyl) or multiple condensed rings (*e.g.*, naphthyl or anthryl). In some embodiments, aryl groups contain 6-14 carbons, and in others from 6 to 12 or even 6 to 10 carbon atoms in the ring portions of the groups. Particular aryls include, but are not limited to, phenyl, naphthyl and the like.

[0054] A "heteroaryl" group is an aryl ring system having one to four heteroatoms as ring atoms in a heteroaromatic ring system, wherein the remainder of the atoms are carbon atoms. In some embodiments, heteroaryl groups contain 5 to 6 ring atoms, and in others from 6 to 9 or even 6 to 10 atoms in the ring portions of the groups. Suitable heteroatoms include oxygen, sulfur and nitrogen. In certain embodiments, the heteroaryl ring system is monocyclic or bicyclic. Examples include, but are not limited to, groups such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl (*e.g.*,

1,2,4-thiadiazolyl), pyrrolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiophenyl, benzothiophenyl, furanyl, benzofuranyl, indolyl, azaindolyl (for example, pyrrolopyridyl or 1H-pyrrolo[2,3-b]pyridyl), indazolyl, benzimidazolyl (for example, 1H-benzo[d]imidazolyl), imidazopyridyl, pyrazolopyridyl, triazolopyridyl, benzotriazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, isoxazolopyridyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups.

[0055] A "partially unsaturated or aromatic heterocycle" is a partially unsaturated or aromatic ring system having one to four heteroatoms as ring atoms in a heteroaromatic ring system, wherein the remainder of the atoms are carbon atoms. If the "partially unsaturated or aromatic heterocycle" is an aromatic heterocycle, then the aromatic heterocycle is a "heteroaryl" as defined above. In one embodiment the partially unsaturated or aromatic heterocycle is a partially unsaturated or aromatic 5- or 6-membered heterocycle. Examples of partially unsaturated heterocycles include, but are not limited to, groups such as 2,5-dihydro-1H-pyrrolyl, 2,5-dihydrofuranyl, 2,5-dihydrothiophenyl, 4,5-dihydrooxazolyl, 4,5-dihydrothiazolyl, 4,5-dihydro-1H-imidazolyl, 4,5-dihydro-1H-1,2,3-triazolyl, 1,2,5,6-tetrahydropyridinyl, and 1,4,5,6-tetrahydropyrimidinyl groups.

[0056] A "heterocycloalkyl" group is a non-aromatic cycloalkyl in which one to four of the ring carbon atoms are independently replaced with a heteroatom from the group consisting of O, S and N. Examples of a heterocycloalkyl group include, but are not limited to, morpholinyl, pyrrolidinyl, piperazinyl, (1,4)-dioxanyl, and (1,3)-dioxolanyl. Heterocycloalkyls can also be bonded at any ring atom (*i.e.*, at any carbon atom or heteroatom of the heterocyclic ring). In one embodiment, the heterocycloalkyl is a 5- or 6-membered heterocycloalkyl.

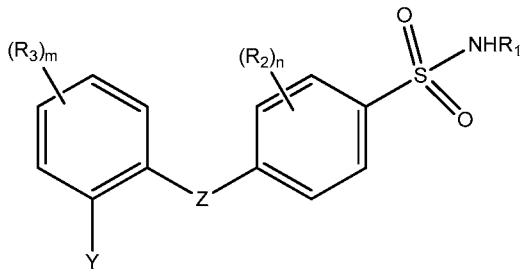
[0057] An "alkyl" group is a saturated straight chain or branched non-cyclic hydrocarbon having, for example, from 1 to 12 carbon atoms, 1 to 9 carbon atoms, 1 to 6 carbon atoms, 1 to 4 carbon atoms, or 2 to 6 carbon atoms. Representative alkyl groups include -methyl, -ethyl, -*n*-propyl, -*n*-butyl, -*n*-pentyl and –*n*-hexyl; while branched alkyls include -isopropyl, -*sec*-butyl, -*iso*-butyl, -*tert*-butyl, -*iso*-pentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,3-dimethylbutyl and the like.

[0058] A "cycloalkyl" group is a saturated cyclic alkyl group of from 3 to 12 carbon atoms having a single cyclic ring or multiple condensed or bridged rings. In some embodiments, the cycloalkyl group has 4 to 12 ring members, whereas in other embodiments the number of ring carbon atoms ranges, for example, from 3 to 5, 3 to 6, or 3 to 7. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like, or multiple or bridged ring structures such as adamantyl and the like.

[0059] A "subject in need thereof" refers to a mammal (*e.g.*, human, dog, horse, or cat) in need of treatment with any method provided herein.

4.2 Compounds

[0060] Provided herein are compounds of Formula (I),



Formula (**I**)

or a pharmaceutically acceptable salt, or a stereoisomeric or tautomeric form thereof, wherein:

Z is -O- or -S-;

Y is –X-C(=O)NR_4R_5, –$(CH_2)_3$-NR_9R_{10}, or 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-(2-yl or 3-yl);

X is (C_6-C_{10})aryl or 5- or 6-membered heteroaryl;

R_1 is a partially unsaturated or aromatic 5- or 6-membered heterocycle;

R_2 is independently at each occurrence –F, -Cl, -Br, -CH_3 or -CN;

R_3 is independently at each occurrence –H, -F, -Cl, -Br, -CF_3, -OCF_3, -CN, (C_1-C_{12})alkyl, or (C_1-C_{12})alkoxy;

R_4 and R_5 are each independently H, (C_1-C_9)alkyl, (C_4-C_{12})cycloalkyl, or R_4 and R_5 together form a 5- to 7-membered heterocycloalkyl ring; with the proviso that:

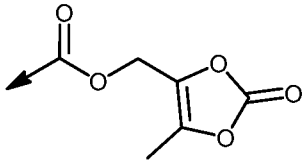
R_4 and R_5 are not both H; and

at least one of R_4 and R_5 independently or said heterocycloalkyl ring formed by R_4 and R_5 together is substituted with 1 or 2 substituents selected from the group consisting of $-CO_2H$, $-CO_2R_6$, -CN, -OH, $-CONR_7R_8$, and $-NR_7R_8$; wherein:

R_6 is $(C_1\text{-}C_{12})$alkyl;

R_7 and R_8 are each independently H, $(C_1\text{-}C_{12})$alkyl, or R_7 and R_8 together form a 4- to 7-membered heterocycloalkyl ring;

R_9 is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, pyrazolyl or pyridinyl; wherein R_9 is optionally further substituted with 1 or 2 substituents selected from the group consisting of -COOH, $-COOR_{11}$, $-CONR_{11}R_{12}$, $-SO_2R_{11}$, $-SO_2NR_{11}R_{12}$, -OH, -CN, $-OR_{11}$, and $-NR_{11}R_{12}$; wherein R_{11} and R_{12} may form a 6 membered heterocycloalkyl ring

R_{10} is R_{11}, $-COR_{11}$, $-COOR_{11}$, $-SO_2R_{11}$, 5-methyl-2-oxo-1,3-dioxol-4-yl,  , $-COO\text{-}CH(CH_3)OCOCH(CH_3)_2$; or R_9 and R_{10} together form a piperazinone or a 4-to 8-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is substituted with 1 or 2 substituents selected from the group consisting of $-COOH$, $-COOR_{11}$, $-CH_2\text{-}COOR_{11}$, -OH, $-NH_2$, -CN, and $(C_1\text{-}C_8)$alkoxy;

R_{11} and R_{12} are independently H or $(C_1\text{-}C_6)$alkyl, optionally substituted with 4- to 8-membered heterocycloalkyl ring; and

m and n are each independently 1, 2, 3, or 4.

[0061] In a certain embodiment, the compounds of Formula (I) are those wherein Y is $-(CH_2)_3\text{-}NR_9R_{10}$.

[0062] In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is an aromatic 5- or 6-membered heterocycle, with 1-3 heteroatoms independently selected from the group consisting of N, O, and S.

[0063] In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is pyridyl or pyrimidinyl.

[0064] In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is an aromatic 5-membered heterocycle with 1 or 2 nitrogen atoms and optionally 1 or 2 sulphur atoms. In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is thiazolyl, isothiazolyl, or thiadiazolyl. In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is thiazolyl. In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is 1,2,4-thiadiazol-5-yl.

[0065] In a particular embodiment, the compounds of Formula (I) are those wherein R_2 is independently at each occurrence –F or -Cl.

[0066] In a particular embodiment, the compounds of Formula (I) are those wherein n is 1, 2, or 3. In a particular embodiment, the compounds of Formula (I) are those wherein n is 2.

[0067] In a particular embodiment, the compounds of Formula (I) are those wherein Z is –O-.

[0068] In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is independently at each occurrence -H, –F, -Cl, or -Br. In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is –H or –Cl. In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is –Cl.

[0069] In a particular embodiment, the compounds of Formula (I) are those wherein m is 1, 2, or 3. In a particular embodiment, the compounds of Formula (I) are those wherein m is 1.

[0070] In a particular embodiment, the compounds of Formula (I) are those wherein R_9 is (C_1-C_6)alkyl; wherein R_9 is optionally further substituted with 1 or 2 substituents selected from the group consisting of -COOH, -COOMe, -$CONH_2$, and –NH_2. In a particular embodiment, the compounds of Formula (I) are those wherein R_9 is methyl or ethyl. In a particular embodiment, the compounds of Formula (I) are those wherein R_9 is further substituted with -COOH.

[0071] In a particular embodiment, the compounds of Formula (I) are those wherein R_{10} is –H, –COMe, -COOEt. In a particular embodiment, the compounds of Formula (I) are those wherein R_{10} is -H or –COMe. In a particular embodiment, the compounds of Formula (I) are those wherein R_{10} is -H.

[0072] In a particular embodiment, the compounds of Formula (I) are those wherein R_9 and R_{10} together form a 4 to 8 membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is substituted with 1 or 2 groups selected from the group consisting of -COOH, –COOMe, –COOEt, -CH_2-COOH, and -NH_2. In a particular embodiment, the compounds of Formula (I) are those wherein R_9 and R_{10} together form a 4 to 8 membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is substituted with 1 or 2 groups selected from the group consisting of –COOH, -CH_2-COOH, and -NH_2.

[0073] In a particular embodiment, the compounds of Formula (I) are those wherein R_9 and R_{10} together form a piperidine substituted with 1 or 2 groups selected from the group consisting of –COOH, –COOMe, –COOEt, -CH_2-COOH, -CH_2-COOMe, -CH_2-COOEt, and -NH_2. In a particular embodiment, the compounds of Formula (I) are those wherein R_9 and R_{10} together form a piperidine substituted with 1 or 2 groups selected from the group consisting of –COOH, -CH_2-COOH, and -NH_2.

[0074] In a certain embodiment, the compounds of Formula (I) are those wherein Y is –X-C(=O)NR_4R_5.

[0075] In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is an aromatic 5- or 6-membered heterocycle, with 1-3 heteroatoms independently selected from the group consisting of N, O, and S.

[0076] In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is pyridyl or pyrimidinyl.

[0077] In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is an aromatic 5-membered heterocycle with 1 or 2 nitrogen atoms and optionally 1 or 2 sulphur atoms. In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is thiazolyl, isothiazolyl, or thiadiazolyl. In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is thiazolyl. In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is 1,2,4-thiadiazol-5-yl.

[0078] In a particular embodiment, the compounds of Formula (I) are those wherein R_2 is independently at each occurrence -F or -Cl.

[0079] In a particular embodiment, the compounds of Formula (I) are those wherein n is 1, 2, or 3. In a particular embodiment, the compounds of Formula (I) are those wherein n is 2.

[0080] In a particular embodiment, the compounds of Formula (I) are those wherein Z is –O-.

[0081] In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is independently at each occurrence -F, -Cl, or -Br. In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is –H or –Cl. In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is –Cl.

[0082] In a particular embodiment, the compounds of Formula (I) are those wherein m is 1, 2, or 3. In a particular embodiment, the compounds of Formula (I) are those wherein m is 1.

[0083] In a particular embodiment, the compounds of Formula (I) are those wherein X is 5- or 6-membered heteroaryl. In a particular embodiment, the compounds of Formula (I) are those wherein X is pyridyl or pyrimidinyl. In a particular embodiment, the compounds of Formula (I) are those wherein X is pyridyl.

[0084] In a particular embodiment, the compounds of Formula (I) are those wherein R_4 is H and R_5 is $(C_1\text{-}C_9)$alkyl.

[0085] In a particular embodiment, the compounds of Formula (I) are those wherein R_5 is methyl or ethyl, substituted with 1 or 2 substituents selected from the group consisting of $-CO_2H$, $-CO_2R_6$, and $-CONR_7R_8$.

[0086] In a particular embodiment, the compounds of Formula (I) are those wherein R_6 is $(C_1\text{-}C_6)$alkyl.

[0087] In a particular embodiment, the compounds of Formula (I) are those wherein R_5 is methyl or ethyl, substituted with $-CO_2H$.

[0088] In a certain embodiment, the compounds of Formula (I) are those wherein Y is 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-(2-yl or 3-yl). In a particular embodiment, the

compounds of Formula (I) are those wherein Y is 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-yl.

[0089] In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is an aromatic 5- or 6-membered heterocycle, with 1-3 heteroatoms independently selected from the group consisting of N, O, and S.

[0090] In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is pyridyl or pyrimidinyl.

[0091] In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is an aromatic 5-membered heterocycle with 1 or 2 nitrogen atoms and optionally 1 or 2 sulphur atoms. In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is thiazolyl, isothiazolyl, or thiadiazolyl. In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is thiazolyl. In a particular embodiment, the compounds of Formula (I) are those wherein R_1 is 1,2,4-thiadiazol-5-yl.

[0092] In a particular embodiment, the compounds of Formula (I) are those wherein R_2 is independently at each occurrence -F or -Cl.

[0093] In a particular embodiment, the compounds of Formula (I) are those wherein n is 1, 2, or 3. In a particular embodiment, the compounds of Formula (I) are those wherein n is 2.

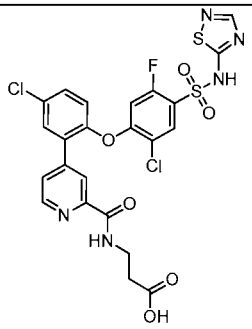
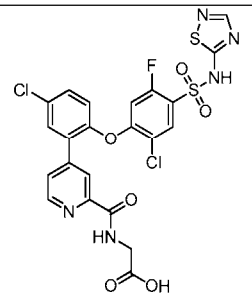
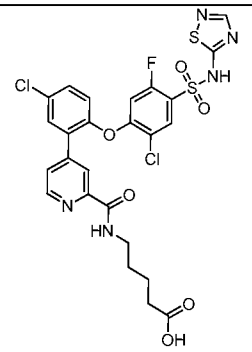
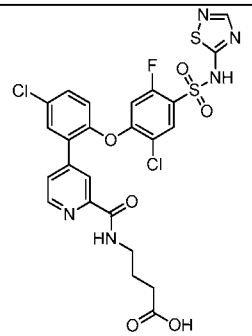
[0094] In a particular embodiment, the compounds of Formula (I) are those wherein Z is –O-.

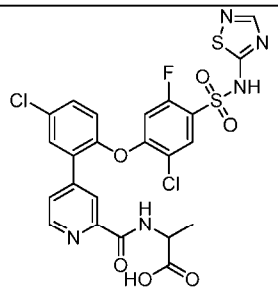
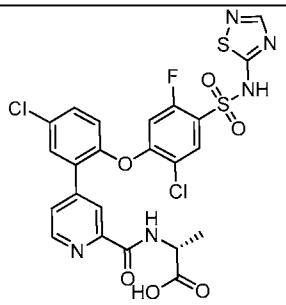
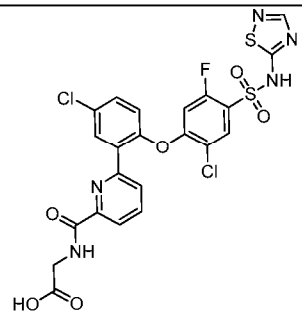
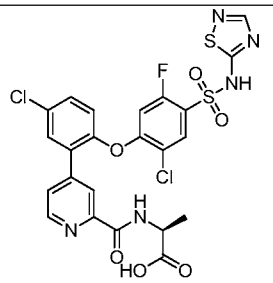
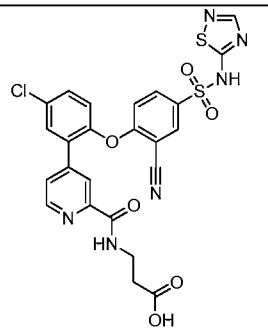
[0095] In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is independently at each occurrence -F, -Cl, or -Br. In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is –H or –Cl. In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is –Cl.

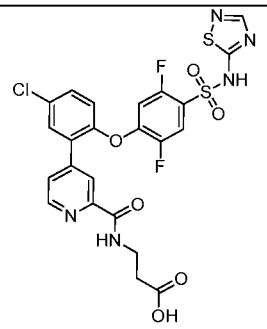
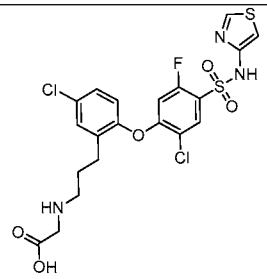
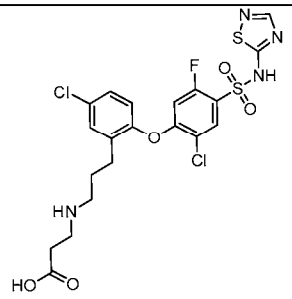
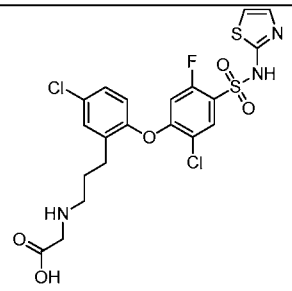
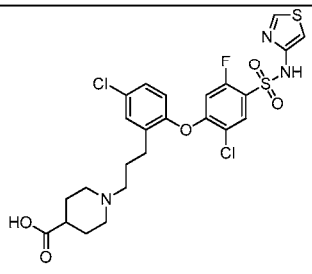
[0096] In a particular embodiment, the compounds of Formula (I) are those wherein m is 1, 2, or 3. In a particular embodiment, the compounds of Formula (I) are those wherein m is 1.

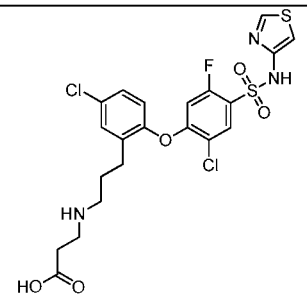
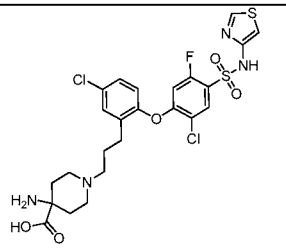
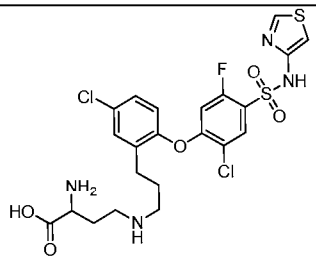
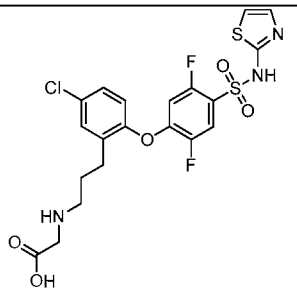
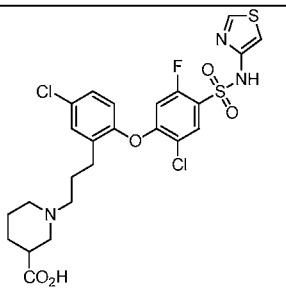
[0097] In a certain embodiment, the compounds of Formula (I) are those wherein the compound is selected from the group consisting of the compounds in Table 1 or a pharmaceutically acceptable salt, or a stereoisomeric or tautomeric form thereof.

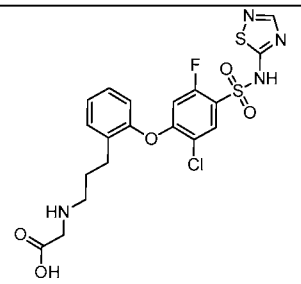
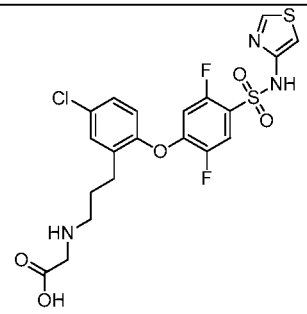
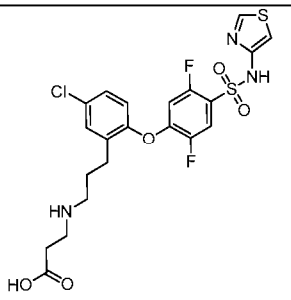
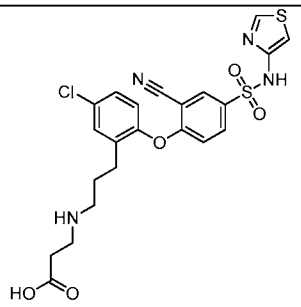
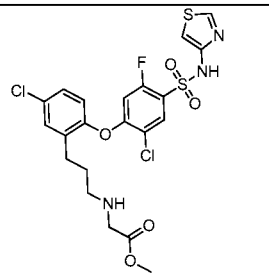
[0098] **Table 1**

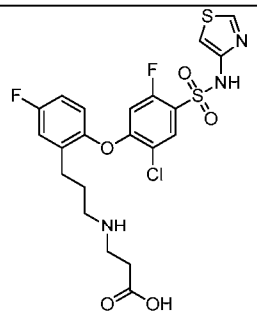
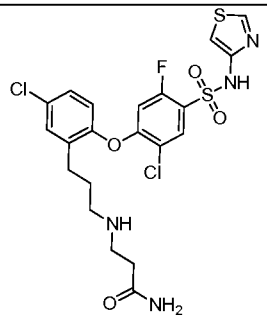
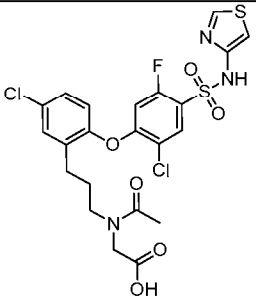
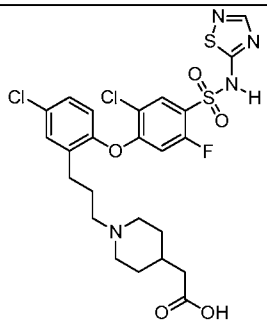
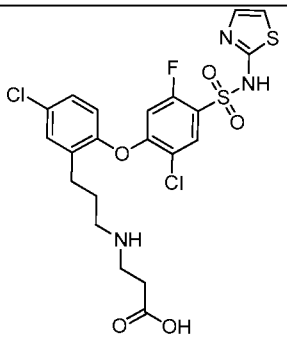
Example	Compound structure	Chemical name*
1		3-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid
2		2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)acetic acid
3		5-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)pentanoic acid
4		4-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)butanoic acid

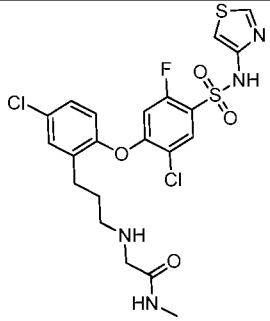
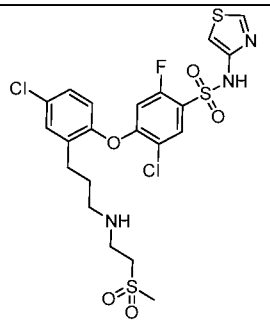
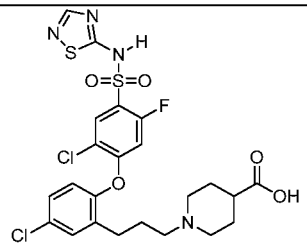
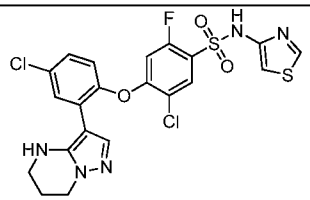
Example	Compound structure	Chemical name*
5		2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid
6		(R)-2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid
7		2-(6-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)acetic acid
8		(S)-2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid
9		3-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-cyanophenoxy)-5-chlorophenyl)picolinamido)propanoic acid

Example	Compound structure	Chemical name*
10		3-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2,5-difluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid
11		2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid
12		3-((3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)amino)propanoic acid
13		2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid
14		1-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)piperidine-4-carboxylic acid

Example	Compound structure	Chemical name*
15		3-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid
16		4-amino-1-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)piperidine-4-carboxylic acid
17		2-amino-4-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)butanoic acid
18		2-((3-(5-chloro-2-(2,5-difluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid
19		1-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)piperidine-3-carboxylic acid

Example	Compound structure	Chemical name*
20		2-((3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)phenyl)propyl)amino)acetic acid
21		2-((3-(5-chloro-2-(2,5-difluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid
22		3-((3-(5-chloro-2-(2,5-difluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid
23		3-((3-(5-chloro-2-(2-cyano-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid
24		methyl 2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetate

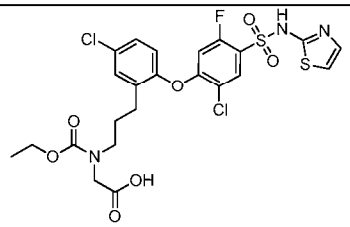
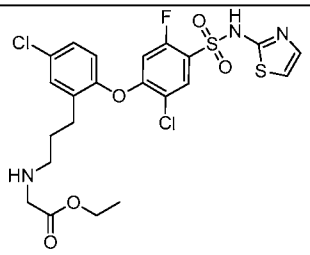
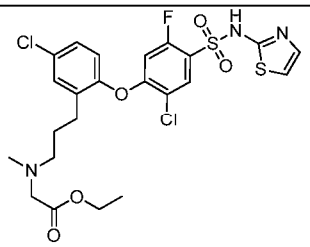
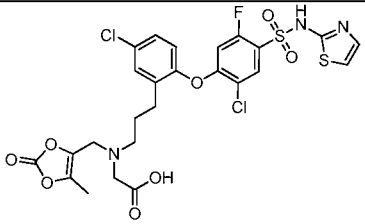
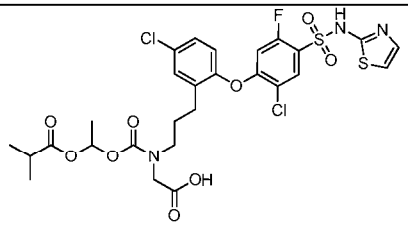
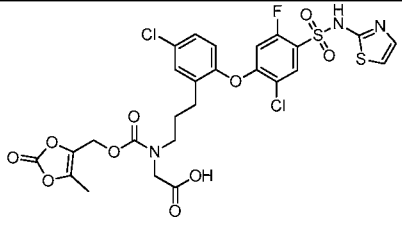
Example	Compound structure	Chemical name*
25		3-((3-(2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)-5-fluorophenyl)propyl)amino)propanoic acid
26		3-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanamide
27		2-(N-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)acetamido)acetic acid
28		2-(1-(3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)piperidin-4-yl)acetic acid
29		3-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid

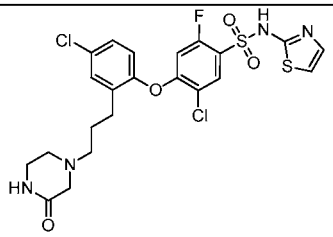
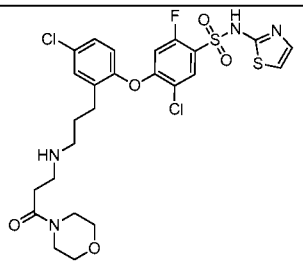
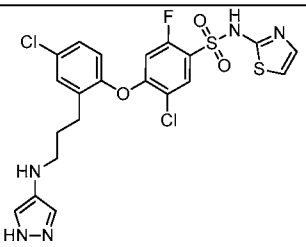
Example	Compound structure	Chemical name*
30		2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)-N-methylacetamide
31		5-chloro-4-(4-chloro-2-(3-((2-(methylsulfonyl)ethyl)amino)propyl)phenoxy)-2-fluoro-N-(thiazol-4-yl)benzenesulfonamide
32		1-(3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)piperidine-4-carboxylic acid
33		5-chloro-4-(4-chloro-2-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl)phenoxy)-2-fluoro-N-(thiazol-4-yl)benzenesulfonamide

* Chemical Names automatically generated with ChemDraw Ultra, Version 12.0.

[0099] In a certain embodiment, the compounds of Formula (I) are those wherein the compound is selected from the group consisting of the compounds in Table 2 or a pharmaceutically acceptable salt, or a stereoisomeric or tautomeric form thereof.

[00100] Table 2

Prophetic Example	Compound structure	Chemical name*
34		2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)(ethoxycarbonyl)amino)acetic acid
35		ethyl 2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetate
36		ethyl 2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)(methyl)amino)acetate
37		2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl)amino)acetic acid
38		2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)((1-(isobutyryloxy)ethoxy)carbonyl)amino)acetic acid
39		2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)(((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)amino)acetic acid

Prophetic Example	Compound structure	Chemical name*
40		5-chloro-4-(4-chloro-2-(3-(3-oxopiperazin-1-yl)propyl)phenoxy)-2-fluoro-N-(thiazol-2-yl)benzenesulfonamide
41		5-chloro-4-(4-chloro-2-(3-((3-morpholino-3-oxopropyl)amino)propyl)phenoxy)-2-fluoro-N-(thiazol-2-yl)benzenesulfonamide
42		4-(2-(3-((1H-pyrazol-4-yl)amino)propyl)-4-chlorophenoxy)-5-chloro-2-fluoro-N-(thiazol-2-yl)benzenesulfonamide

* Chemical Names automatically generated with ChemDraw Ultra, Version 12.0.

[00101] For the proposes of this disclosure, Table 1 and Table 2 serve to define that a particular structure is associated with a particular name. Whenever a particular name is recited in this disclosure or the claims, the chemical structure associated with that particular name shall be the structure identified in Table 1 or Table 2.

[00102] In a particular embodiment, the compounds of Formula (I) are those wherein the compound is

2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)acetic acid,

3-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid,

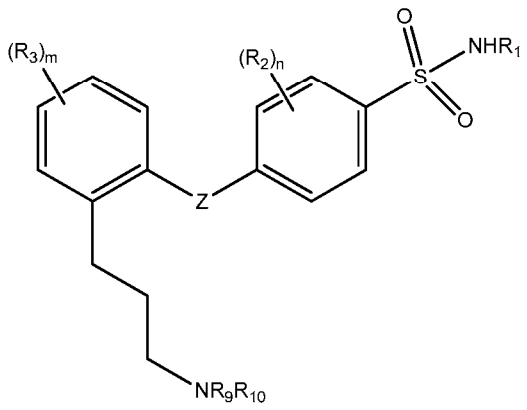
2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid, or

3-((3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-

chlorophenyl)propyl)amino)propanoic acid;

or a pharmaceutically acceptable salt, or a stereoisomeric or tautomeric form thereof.

[00103] Further provided herein are compounds of Formula (Ia),



Formula (Ia)

or a pharmaceutically acceptable salt, or a stereoisomeric or tautomeric form thereof, wherein:

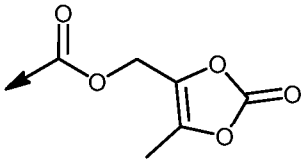
Z is -O- or -S-;

R_1 is a partially unsaturated or aromatic 5- or 6-membered heterocycle;

R_2 is independently at each occurrence –F, -Cl, -Br, $-CH_3$ or -CN;

R_3 is independently at each occurrence –H, -F, -Cl, -Br, $-CF_3$, $-OCF_3$, -CN, $(C_1\text{-}C_{12})$alkyl, or $(C_1\text{-}C_{12})$alkoxy;

R_9 is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, pyrazolyl or pyridinyl; wherein R_9 is optionally further substituted with 1 or 2 substituents selected from the group consisting of -COOH, $-COOR_{11}$, $-CONR_{11}R_{12}$, $-SO_2R_{11}$, $-SO_2NR_{11}R_{12}$, -OH, -CN, $-OR_{11}$, and $-NR_{11}R_{12}$; wherein R_{11} and R_{12} may form a 6 membered heterocycloalkyl ring

R_{10} is R_{11}, $-COR_{11}$, $-COOR_{11}$, $-SO_2R_{11}$, 5-methyl-2-oxo-1,3-dioxol-4-yl,  , $-COO\text{-}CH(CH_3)OCOCH(CH_3)_2$; or R_9 and R_{10} together form a piperazinone or a 4-to 8-membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is substituted with 1 or 2 substituents selected from the group consisting of –COOH, $-COOR_{11}$, $-CH_2\text{-}COOR_{11}$, -OH, $-NH_2$, -CN, and $(C_1\text{-}C_8)$alkoxy;

R_{11} and R_{12} are independently H or (C_1-C_6)alkyl, optionally substituted with 4- to 8-membered heterocycloalkyl ring; and

m and n are each independently 1, 2, 3, or 4.

[00104] In a particular embodiment, the compounds of Formula (Ia) are those wherein R_1 is an aromatic 5- or 6-membered heterocycle, with 1-3 heteroatoms independently selected from the group consisting of N, O, and S.

[00105] In a particular embodiment, the compounds of Formula (Ia) are those wherein R_1 is pyridyl or pyrimidinyl.

[00106] In a particular embodiment, the compounds of Formula (Ia) are those wherein R_1 is an aromatic 5-membered heterocycle with 1 or 2 nitrogen atoms and optionally 1 or 2 sulphur atoms. In a particular embodiment, the compounds of Formula (Ia) are those wherein R_1 is thiazolyl, isothiazolyl, or thiadiazolyl. In a particular embodiment, the compounds of Formula (Ia) are those wherein R_1 is thiazolyl. In a particular embodiment, the compounds of Formula (Ia) are those wherein R_1 is 1,2,4-thiadiazol-5-yl.

[00107] In a particular embodiment, the compounds of Formula (Ia) are those wherein R_2 is independently at each occurrence –F or -Cl.

[00108] In a particular embodiment, the compounds of Formula (Ia) are those wherein n is 1, 2, or 3. In a particular embodiment, the compounds of Formula (Ia) are those wherein n is 2.

[00109] In a particular embodiment, the compounds of Formula (Ia) are those wherein Z is –O-.

[00110] In a particular embodiment, the compounds of Formula (Ia) are those wherein R_3 is independently at each occurrence -H, –F, -Cl, or -Br. In a particular embodiment, the compounds of Formula (Ia) are those wherein R_3 is –H or –Cl. In a particular embodiment, the compounds of Formula (Ia) are those wherein R_3 is –Cl.

[00111] In a particular embodiment, the compounds of Formula (Ia) are those wherein m is 1, 2, or 3. In a particular embodiment, the compounds of Formula (Ia) are those wherein m is 1.

[00112] In a particular embodiment, the compounds of Formula (Ia) are those wherein R_9 is (C_1-C_6)alkyl; wherein R_9 is optionally further substituted with 1 or 2 substituents selected from the group consisting of -COOH, -COOMe, -$CONH_2$, and –NH_2. In a particular embodiment, the compounds of Formula (Ia) are those wherein R_9 is methyl or ethyl. In a particular embodiment, the compounds of Formula (Ia) are those wherein R_9 is further substituted with -COOH.

[00113] In a particular embodiment, the compounds of Formula (Ia) are those wherein R_{10} is –H, –COMe, -COOEt. In a particular embodiment, the compounds of Formula (Ia) are those wherein R_{10} is -H or –COMe. In a particular embodiment, the compounds of Formula (Ia) are those wherein R_{10} is -H.

[00114] In a particular embodiment, the compounds of Formula (Ia) are those wherein R_9 and R_{10} together form a 4 to 8 membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is substituted with 1 or 2 groups selected from the group consisting of -COOH, –COOMe, –COOEt, -CH_2-COOH, and -NH_2. In a particular embodiment, the compounds of Formula (I) are those wherein R_9 and R_{10} together form a 4 to 8 membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is substituted with 1 or 2 groups selected from the group consisting of –COOH, -CH_2-COOH, and -NH_2.

[00115] In a particular embodiment, the compounds of Formula (Ia) are those wherein R_9 and R_{10} together form a piperidine substituted with 1 or 2 groups selected from the group consisting of –COOH, –COOMe, –COOEt, -CH_2-COOH, -CH_2-COOMe, -CH_2-COOEt, and -NH_2. In a particular embodiment, the compounds of Formula (Ia) are those wherein R_9 and R_{10} together form a piperidine substituted with 1 or 2 groups selected from the group consisting of –COOH, -CH_2-COOH, and -NH_2.

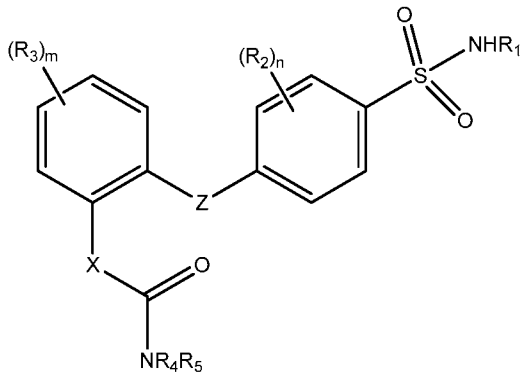
[00116] In a particular embodiment, the compounds of Formula (Ia) are selected from the group consisting of
2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid,
3-((3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)amino)propanoic acid,
2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-

yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid,
1-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)piperidine-4-carboxylic acid,
3-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid,
4-amino-1-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)piperidine-4-carboxylic acid,
2-amino-4-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)butanoic acid,
2-((3-(5-chloro-2-(2,5-difluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid,
1-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)piperidine-3-carboxylic acid,
2-((3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)phenyl)propyl)amino)acetic acid,
2-((3-(5-chloro-2-(2,5-difluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid,
3-((3-(5-chloro-2-(2,5-difluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid,
3-((3-(5-chloro-2-(2-cyano-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid,
methyl 2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetate,
3-((3-(2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)-5-fluorophenyl)propyl)amino)propanoic acid,
3-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanamide,
2-(N-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)acetamido)acetic acid,
2-(1-(3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)piperidin-4-yl)acetic acid,

3-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid,
2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)-N-methylacetamide,
5-chloro-4-(4-chloro-2-(3-((2-(methylsulfonyl)ethyl)amino)propyl)phenoxy)-2-fluoro-N-(thiazol-4-yl)benzenesulfonamide, and
1-(3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)piperidine-4-carboxylic acid;
or a pharmaceutically acceptable salt, or a stereoisomeric or tautomeric form thereof.

[00117] In a particular embodiment, the compounds of Formula (Ia) are selected from the group comprising
2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)(ethoxycarbonyl)amino)acetic acid,
ethyl 2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetate,
ethyl 2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)(methyl)amino)acetate,
2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)((5-methyl-2-oxo-1,3-dioxol-4-yl)methyl)amino)acetic acid,
2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)((1-(isobutyryloxy)ethoxy)carbonyl)amino)acetic acid,
2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)(((5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy)carbonyl)amino)acetic acid,
5-chloro-4-(4-chloro-2-(3-(3-oxopiperazin-1-yl)propyl)phenoxy)-2-fluoro-N-(thiazol-2-yl)benzenesulfonamide,
5-chloro-4-(4-chloro-2-(3-((3-morpholino-3-oxopropyl)amino)propyl)phenoxy)-2-fluoro-N-(thiazol-2-yl)benzenesulfonamide, and
4-(2-(3-((1H-pyrazol-4-yl)amino)propyl)-4-chlorophenoxy)-5-chloro-2-fluoro-N-(thiazol-2-yl)benzenesulfonamide;
or a pharmaceutically acceptable salt, or a stereoisomeric or tautomeric form thereof.

[00118] Provided herein are compounds of Formula (Ib),



Formula (Ib)

or a pharmaceutically acceptable salt, or a stereoisomeric or tautomeric form thereof, wherein:

Z is -O- or -S-;

X is (C_6-C_{10})aryl or 5- or 6-membered heteroaryl;

R_1 is a partially unsaturated or aromatic 5- or 6-membered heterocycle;

R_2 is independently at each occurrence –F, -Cl, -Br, -CH_3 or -CN;

R_3 is independently at each occurrence –H, -F, -Cl, -Br, -CF_3, -OCF_3, -CN, (C_1-C_{12})alkyl, or (C_1-C_{12})alkoxy;

R_4 and R_5 are each independently H, (C_1-C_9)alkyl, (C_4-C_{12})cycloalkyl, or R_4 and R_5 together form a 5- to 7-membered heterocycloalkyl ring; with the proviso that:

R_4 and R_5 are not both H; and

at least one of R_4 and R_5 independently or said heterocycloalkyl ring formed by R_4 and R_5 together is substituted with 1 or 2 substituents selected from the group consisting of –CO_2H, -CO_2R_6, -CN, -OH, -$CONR_7R_8$, and -NR_7R_8; wherein:

R_6 is (C_1-C_{12})alkyl;

R_7 and R_8 are each independently H, (C_1-C_{12})alkyl, or R_7 and R_8 together form a 4- to 7-membered heterocycloalkyl ring; and

m and n are each independently 1, 2, 3, or 4.

[00119] In a particular embodiment, the compounds of Formula (Ib) are those wherein R_1 is an aromatic 5- or 6-membered heterocycle, with 1-3 heteroatoms independently selected from the group consisting of N, O, and S.

[00120] In a particular embodiment, the compounds of Formula (Ib) are those wherein R_1 is pyridyl or pyrimidinyl.

[00121] In a particular embodiment, the compounds of Formula (Ib) are those wherein R_1 is an aromatic 5-membered heterocycle with 1 or 2 nitrogen atoms and optionally 1 or 2 sulphur atoms. In a particular embodiment, the compounds of Formula (Ib) are those wherein R_1 is thiazolyl, isothiazolyl, or thiadiazolyl. In a particular embodiment, the compounds of Formula (Ib) are those wherein R_1 is thiazolyl. In a particular embodiment, the compounds of Formula (Ib) are those wherein R_1 is 1,2,4-thiadiazol-5-yl.

[00122] In a particular embodiment, the compounds of Formula (Ib) are those wherein R_2 is independently at each occurrence -F or -Cl.

[00123] In a particular embodiment, the compounds of Formula (Ib) are those wherein n is 1, 2, or 3. In a particular embodiment, the compounds of Formula (Ib) are those wherein n is 2.

[00124] In a particular embodiment, the compounds of Formula (Ib) are those wherein Z is –O-.

[00125] In a particular embodiment, the compounds of Formula (Ib) are those wherein R_3 is independently at each occurrence -F, -Cl, or -Br. In a particular embodiment, the compounds of Formula (Ib) are those wherein R_3 is –H or –Cl. In a particular embodiment, the compounds of Formula (Ib) are those wherein R_3 is –Cl.

[00126] In a particular embodiment, the compounds of Formula (Ib) are those wherein m is 1, 2, or 3. In a particular embodiment, the compounds of Formula (Ib) are those wherein m is 1.

[00127] In a particular embodiment, the compounds of Formula (Ib) are those wherein X is 5- or 6-membered heteroaryl. In a particular embodiment, the compounds of Formula (Ib) are those wherein X is pyridyl or pyrimidinyl. In a particular embodiment, the compounds of Formula (Ib) are those wherein X is pyridyl.

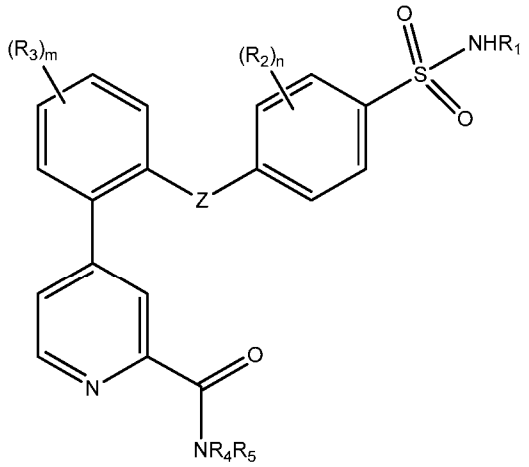
[00128] In a particular embodiment, the compounds of Formula (Ib) are those wherein R_4 is H and R_5 is (C_1-C_9)alkyl.

[00129] In a particular embodiment, the compounds of Formula (Ib) are those wherein R_5 is methyl or ethyl, substituted with 1 or 2 substituents selected from the group consisting of $-CO_2H$, $-CO_2R_6$, and $-CONR_7R_8$.

[00130] In a particular embodiment, the compounds of Formula (Ib) are those wherein R_6 is $(C_1\text{-}C_6)$alkyl.

[00131] In a particular embodiment, the compounds of Formula (Ib) are those wherein R_5 is methyl or ethyl, substituted with $-CO_2H$.

[00132] Provided herein are compounds of Formula (Ic),



Formula (Ic)

or a pharmaceutically acceptable salt, or a stereoisomeric or tautomeric form thereof, wherein:

Z is -O- or -S-;

R_1 is a partially unsaturated or aromatic 5- or 6-membered heterocycle;

R_2 is independently at each occurrence –F, -Cl, -Br, $-CH_3$ or -CN;

R_3 is independently at each occurrence –H, -F, -Cl, -Br, $-CF_3$, $-OCF_3$, -CN, $(C_1\text{-}C_{12})$alkyl, or $(C_1\text{-}C_{12})$alkoxy;

R_4 and R_5 are each independently H, $(C_1\text{-}C_9)$alkyl, $(C_4\text{-}C_{12})$cycloalkyl, or R_4 and R_5 together form a 5- to 7-membered heterocycloalkyl ring; with the proviso that:

R_4 and R_5 are not both H; and

at least one of R_4 and R_5 independently or said heterocycloalkyl ring formed by R_4 and R_5 together is substituted with 1 or 2 substituents selected from the group consisting of $-CO_2H$, $-CO_2R_6$, -CN, -OH, $-CONR_7R_8$, and $-NR_7R_8$; wherein:

R_6 is $(C_1$-$C_{12})$alkyl;

R_7 and R_8 are each independently H, $(C_1$-$C_{12})$alkyl, or R_7 and R_8 together form a 4- to 7-membered heterocycloalkyl ring; and

m and n are each independently 1, 2, 3, or 4.

[00133] In a particular embodiment, the compounds of Formula (Ic) are those wherein R_1 is an aromatic 5- or 6-membered heterocycle, with 1-3 heteroatoms independently selected from the group consisting of N, O, and S.

[00134] In a particular embodiment, the compounds of Formula (Ic) are those wherein R_1 is pyridyl or pyrimidinyl.

[00135] In a particular embodiment, the compounds of Formula (Ic) are those wherein R_1 is an aromatic 5-membered heterocycle with 1 or 2 nitrogen atoms and optionally 1 or 2 sulphur atoms. In a particular embodiment, the compounds of Formula (Ic) are those wherein R_1 is thiazolyl, isothiazolyl, or thiadiazolyl. In a particular embodiment, the compounds of Formula (Ic) are those wherein R_1 is thiazolyl. In a particular embodiment, the compounds of Formula (Ic) are those wherein R_1 is 1,2,4-thiadiazol-5-yl.

[00136] In a particular embodiment, the compounds of Formula (Ic) are those wherein R_2 is independently at each occurrence -F or -Cl.

[00137] In a particular embodiment, the compounds of Formula (Ic) are those wherein n is 1, 2, or 3. In a particular embodiment, the compounds of Formula (Ic) are those wherein n is 2.

[00138] In a particular embodiment, the compounds of Formula (Ic) are those wherein Z is –O-.

[00139] In a particular embodiment, the compounds of Formula (Ic) are those wherein R_3 is independently at each occurrence -F, -Cl, or -Br. In a particular embodiment, the compounds of Formula (I) are those wherein R_3 is –H or –Cl. In a particular embodiment, the compounds of Formula (Ic) are those wherein R_3 is –Cl.

[00140] In a particular embodiment, the compounds of Formula (Ic) are those wherein m is 1, 2, or 3. In a particular embodiment, the compounds of Formula (Ic) are those wherein m is 1.

[00141] In a particular embodiment, the compounds of Formula (Ic) are those wherein X is 5- or 6-membered heteroaryl. In a particular embodiment, the compounds of Formula (Ic) are those wherein X is pyridyl or pyrimidinyl. In a particular embodiment, the compounds of Formula (Ic) are those wherein X is pyridyl.

[00142] In a particular embodiment, the compounds of Formula (Ic) are those wherein R_4 is H and R_5 is $(C_1\text{-}C_9)$alkyl.

[00143] In a particular embodiment, the compounds of Formula (Ic) are those wherein R_5 is methyl or ethyl, substituted with 1 or 2 substituents selected from the group consisting of $-CO_2H$, $-CO_2R_6$, and $-CONR_7R_8$.

[00144] In a particular embodiment, the compounds of Formula (Ic) are those wherein R_6 is $(C_1\text{-}C_6)$alkyl.

[00145] In a particular embodiment, the compounds of Formula (Ic) are those wherein R_5 is methyl or ethyl, substituted with $-CO_2H$.

[00146] In a particular embodiment, the compounds of Formula (Ic) are selected from the group consisting of
3-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid,
2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)acetic acid,
5-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)pentanoic acid,
4-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)butanoic acid,
2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid,

(R)-2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid,

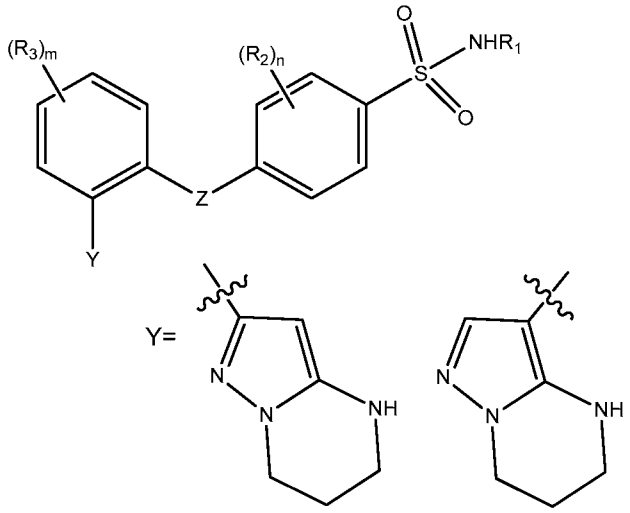
(S)-2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid,

3-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-cyanophenoxy)-5-chlorophenyl)picolinamido)propanoic acid, and

3-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2,5-difluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid; or

a pharmaceutically acceptable salt, or a stereoisomeric or tautomeric form thereof.

[00147] Provided herein are compounds of Formula (Id),



Formula (Id)

or a pharmaceutically acceptable salt, or a stereoisomeric or tautomeric form thereof, wherein:

Y is 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-(2-yl or 3-yl);

Z is -O- or -S-;

R_1 is a partially unsaturated or aromatic 5- or 6-membered heterocycle;

R_2 is independently at each occurrence –F, -Cl, -Br, $-CH_3$ or -CN;

R_3 is independently at each occurrence –H, -F, -Cl, -Br, $-CF_3$, $-OCF_3$, -CN, $(C_1\text{-}C_{12})$alkyl, or $(C_1\text{-}C_{12})$alkoxy; and

m and n are each independently 1, 2, 3, or 4.

[00148] In a certain embodiment, the compounds of Formula (Id) are those wherein Y is 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-(2-yl or 3-yl). In a particular embodiment, the compounds of Formula (Id) are those wherein Y is 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-yl.

[00149] In a particular embodiment, the compounds of Formula (Id) are those wherein R_1 is an aromatic 5- or 6-membered heterocycle, with 1-3 heteroatoms independently selected from the group consisting of N, O, and S.

[00150] In a particular embodiment, the compounds of Formula (Id) are those wherein R_1 is pyridyl or pyrimidinyl.

[00151] In a particular embodiment, the compounds of Formula (Id) are those wherein R_1 is an aromatic 5-membered heterocycle with 1 or 2 nitrogen atoms and optionally 1 or 2 sulphur atoms. In a particular embodiment, the compounds of Formula (Id) are those wherein R_1 is thiazolyl, isothiazolyl, or thiadiazolyl. In a particular embodiment, the compounds of Formula (Id) are those wherein R_1 is thiazolyl. In a particular embodiment, the compounds of Formula (Id) are those wherein R_1 is 1,2,4-thiadiazol-5-yl.

[00152] In a particular embodiment, the compounds of Formula (Id) are those wherein R_2 is independently at each occurrence -F or -Cl.

[00153] In a particular embodiment, the compounds of Formula (Id) are those wherein n is 1, 2, or 3. In a particular embodiment, the compounds of Formula (Id) are those wherein n is 2.

[00154] In a particular embodiment, the compounds of Formula (Id) are those wherein Z is –O-.

[00155] In a particular embodiment, the compounds of Formula (Id) are those wherein R_3 is independently at each occurrence -F, -Cl, or -Br. In a particular embodiment, the compounds of Formula (Id) are those wherein R_3 is –H or –Cl. In a particular embodiment, the compounds of Formula (Id) are those wherein R_3 is –Cl.

[00156] In a particular embodiment, the compounds of Formula (Id) are those wherein m is 1, 2, or 3. In a particular embodiment, the compounds of Formula (Id) are those wherein m is 1.

[00157] In a particular embodiment, the compound of Formula (Id) is 5-chloro-4-(4-chloro-2-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl)phenoxy)-2-fluoro-N-(thiazol-4-yl)benzenesulfonamide; or a pharmaceutically acceptable salt, or a stereoisomeric or tautomeric form thereof.

[00158] It should also be noted the Compounds provided herein can contain unnatural proportions of atomic isotopes at one or more of the atoms. For example, the Compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I), sulfur-35 (^{35}S), or carbon-14 (^{14}C), or may be isotopically enriched, such as with deuterium (^{2}H), carbon-13 (^{13}C), or nitrogen-15 (^{15}N). As used herein, an "isotopologue" is an isotopically enriched Compound. The term "isotopically enriched" refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. "Isotopically enriched" may also refer to a Compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom. The term "isotopic composition" refers to the amount of each isotope present for a given atom. Radiolabeled and isotopically enriched Compounds are useful as therapeutic agents, *e.g.*, cancer and inflammation therapeutic agents; research reagents, *e.g.*, binding assay reagents; and diagnostic agents, *e.g.*, *in vivo* imaging agents. All isotopic variations of the Compounds as described herein, whether radioactive or not, are intended to be encompassed within the scope of the embodiments provided herein. In some embodiments, there are provided isotopologues of the Compounds, for example, the isotopologues are deuterium, carbon-13, or nitrogen-15 enriched Compounds.

[00159] In certain embodiments, a Compound provided herein modulates the activity of a sodium ion channel, such as a voltage-gated sodium ion channel. In more specific embodiments, such a voltage-gated sodium ion channel is NaV1.7 (whose alpha subunit is encoded by the human gene SCN9A).

[00160] In certain embodiments, a Compound provided herein reduces the sodium ion flux through NaV1.7 by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 98%, 99%,

or 100%, or by ranges between any of the recited percentages (*e.g.*, 10-20%, 10-30%, 10-40%, 20-30%, or 20-40%) relative to the activated channel in the absence of the compound.

[00161] In certain embodiments, a Compound provided herein increases the sodium ion flux through NaV1.7 by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 250%, 500%, 750%, or 1000%, or by ranges between any of the recited percentages (*e.g.*, 10-20%, 10-30%, 10-40%, 20-30%, or 20-40%) relative to the activated channel in the absence of the compound.

[00162] In certain embodiments, a Compound provided herein, desensitizes the response of NaV1.7 to the change in membrane potential such that the channel requires at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or ranges between any of the recited percentages (*e.g.*, 10-20%, 10-30%, 10-40%, 20-30%, or 20-40%) higher change in membrane potential to be activated relative to the channel in the absence of the compound.

[00163] In certain embodiments, a Compound provided herein, sensitizes the response of NaV1.7 to the change in membrane potential such that the channel requires at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or ranges between any of the recited percentages (*e.g.*, 10-20%, 10-30%, 10-40%, 20-30%, or 20-40%) lower change in membrane potential to be activated relative to the channel in the absence of the compound.

[00164] In certain embodiments, a Compound provided herein, affects a voltage-gated sodium ion channel, *e.g.*, NaV1.7, in one or more of the following states: deactivated (closed), activated (open), or inactivated (closed).

[00165] In certain embodiments, a Compound provided herein, affects activation, inactivation, or deinactivation of a voltage-gated sodium ion channel, *e.g.*, NaV1.7.

[00166] In certain embodiments, a Compound provided herein, modulates NaV1.7 specifically, *i.e.*, the compound modulates NaV1.7 to at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 250%, 500%, 750%, or 1000% higher degree than another voltage-gated sodium ion channel (such as NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.8, and/or NaV1.9), or to a higher degree between any of the recited percentages (*e.g.*, 10-20%, 10-30%, 10-40%, 20-30%, or 20-40%) than another voltage-gated sodium channel.

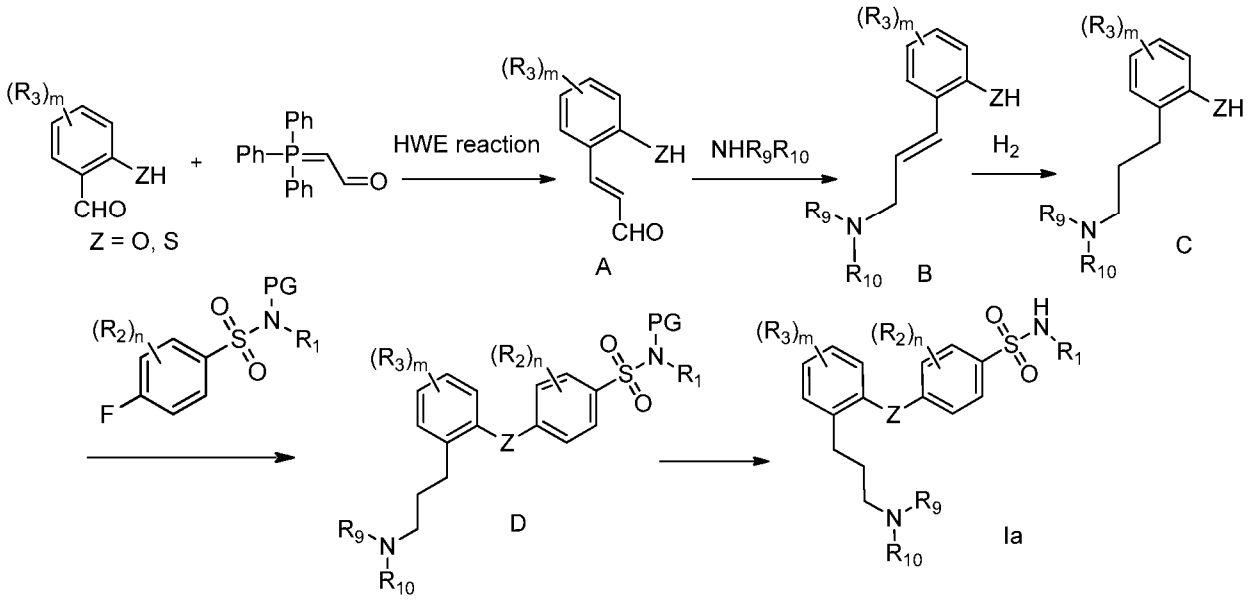
[00167] Any assay known to the skilled artisan can be used to test the effect of a compound provided herein on a voltage-gated sodium ion channel. In certain embodiments, a cell culture assay is used, wherein the voltage-gated sodium ion channel is recombinantly expressed in the cultured cells. In certain more specific embodiments, the alpha subunit of the voltage-gated sodium ion channel is expressed but no accessory proteins are recombinantly expressed in the same cell. In a specific embodiment, SCN9A and SCN9B1 and SCN9B2 are co-expressed in the same cell. In other embodiments, the alpha subunit of the voltage-gated sodium ion channel is expressed and at least one accessory protein (*e.g.*, a beta-subunit) is co-expressed in the same cell.

[00168] In certain embodiments, an FDSS membrane potential assay can be used to test the activity of the voltage-gated sodium ion channel (see the Section entitled "FDSS Membrane Potential *in vitro* Assay" below). In other embodiments, the membrane potential is measured directly using. In certain embodiments, the current through a voltage-gated sodium ion channel is tested using the patch clamp method.

4.3 Methods for Making Compounds

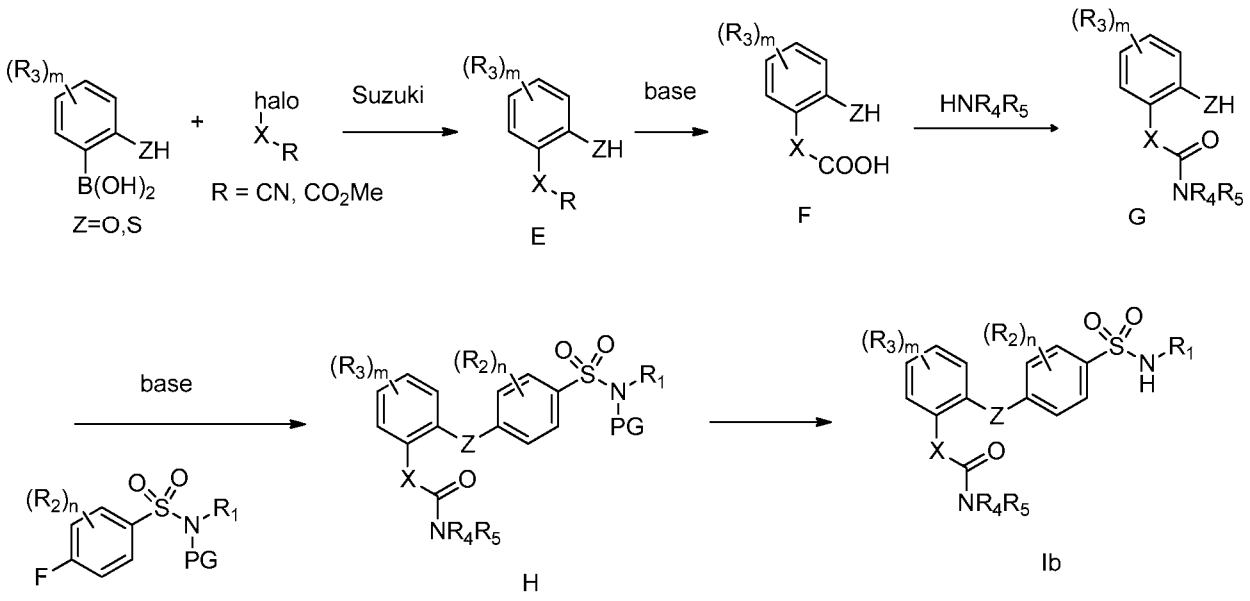
[00169] A compound of Formula (Ia) can be synthesized according to synthetic Scheme 1. An R_3 substituted 2-hydroxybenzaldehyde or 2-mercaptobenzaldehyde is reacted under Horner–Wadsworth–Emmons ("HWE") conditions with formylmethylene-triphenylphosphorane to give an α,β-unsaturated aldehyde, Intermediate A. Intermediate A is reacted with HNR_9R_{10} under reductive amination conditions using, for example, sodium borohydride, to give Intermediate B. Intermediate B is then reduced to give Intermediate C using, for example, hydrogen in the presence of metal catalyst, such as palladium on carbon. Intermediate C is reacted with a fluoro-substituted phenylsulfonamide, wherein the sulfonamide nitrogen is optionally protected by a group ("PG"), such as *tert*-butoxycarbonyl ("BOC") or 2,4-dimethoxybenzyl, in presence of a base, such as potassium carbonate, to give Intermediate D. Deprotection of the sulfonamide group of Intermediate D by using, for example, hydrochloric acid, gives a compound of Formula (Ia).

Scheme 1



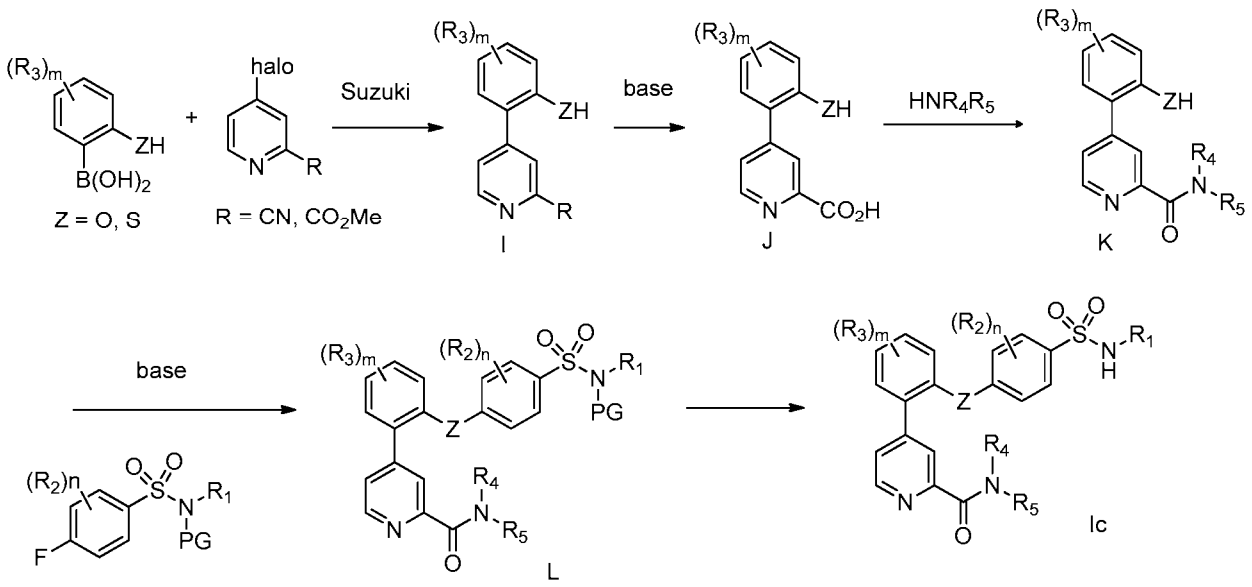
[00170] A compound of Formula (Ib) can be prepared according to synthetic Scheme 2. A Suzuki coupling between an R_3 substituted 2-hydroxy-boronic acid or 2-mercapto-boronic acid and derivative of X, wherein X is, for example, a (C_6-C_{10})aryl or 5- or 6-membered heteroaryl, such as a 4-halo-picolinonitrile or a 4-halo-picolinic ester (*e.g.*, a methyl picolinate), wherein the halo substituent is, for example, a chloro or bromo substituent, provides Intermediate E. Intermediate E is reacted with a base, such as potassium hydroxide, to give Intermediate F. Intermediate F is reacted with NHR_4R_5 to form the amide Intermediate G using, for example, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide ("EDC") and 1-hydroxy-1H-benzotriazole ("HOBt"). Intermediate G is reacted with a fluoro-substituted phenylsulfonamide, wherein the sulfonamide nitrogen is optionally protected by a group, such as BOC or 2,4-dimethoxybenzyl, in presence of a base, such as potassium carbonate, to give Intermediate H. Deprotection of the sulfonamide group of Intermediate H by using, for example, hydrochloric acid, gives a compound of Formula (Ib).

Scheme 2



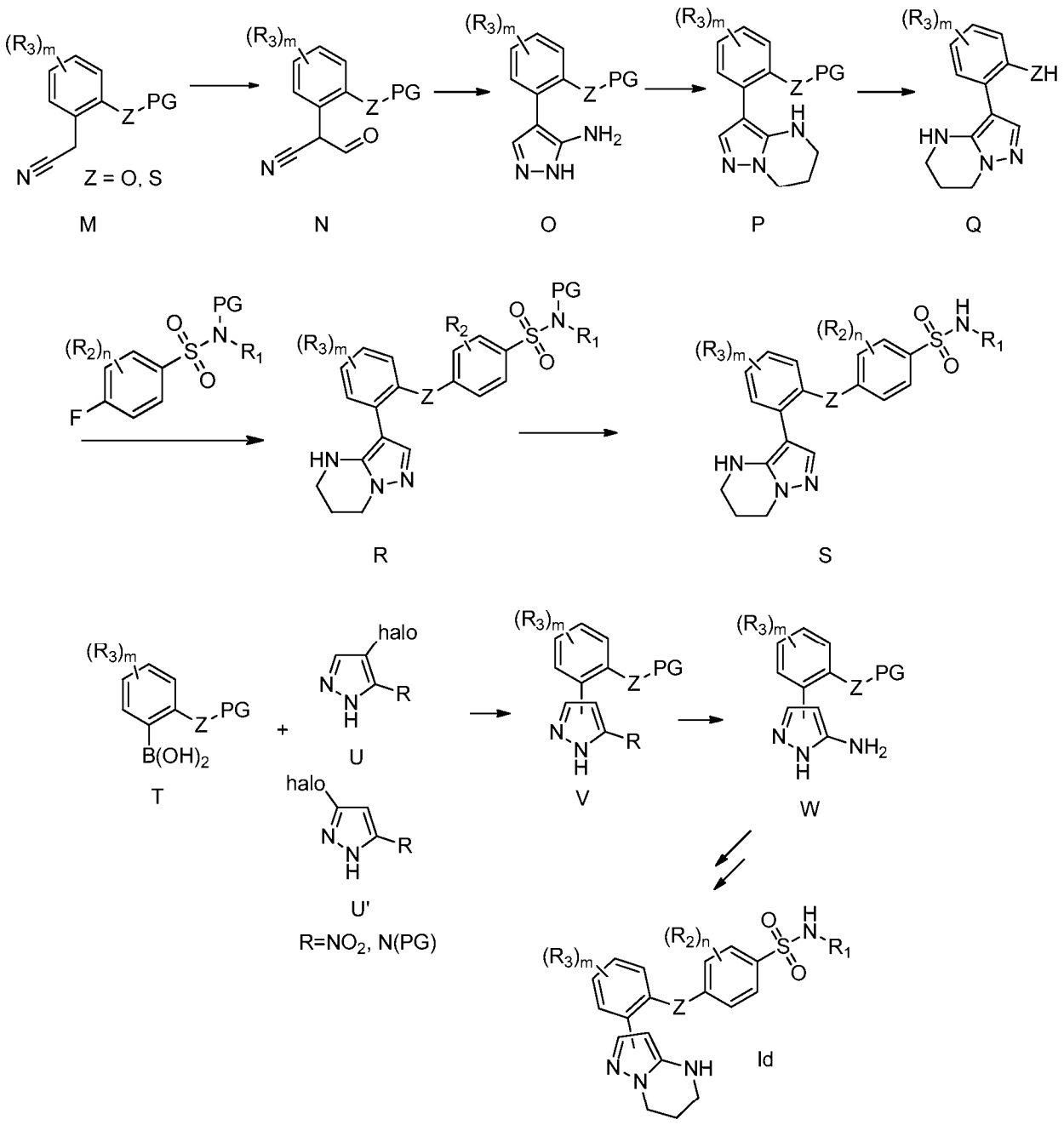
[00171] A compound of Formula (Ic) can be prepared according to synthetic Scheme 3. A Suzuki coupling between an R_3 substituted 2-hydroxy-boronic acid or 2-mercapto-boronic acid and pyridine derivative, such as a 4-halo-picolinonitrile or a 4-halo-picolinic ester (*e.g.*, a methyl picolinate), wherein the halo substituent is, for example, a chloro or bromo substituent, provides Intermediate I. Intermediate I is reacted with a base, such as potassium hydroxide, to give Intermediate J. Intermediate J is reacted with NHR_4R_5 to form the amide Intermediate K using, for example, EDC and HOBt. Intermediate K is reacted with a fluoro-substituted phenylsulfonamide, wherein the sulfonamide nitrogen is optionally protected by a group, such as BOC or 2,4-dimethoxybenzyl, in presence of a base, such as potassium carbonate, to give Intermediate L. Deprotection of the sulfonamide group of Intermediate L by using, for example, hydrochloric acid, gives a compound of Formula (Ic).

Scheme 3



[00172] A compound of Formula (Id) can be prepared according to synthetic Scheme 4. Phenylacetonitrile derivative M with a protected hydroxy or thiol group, such as a methyl protected hydroxy group, *i.e.*, a –OMe group, is formylated by using, for example, Na/ethyl formate or NaOEt/ethyl formate to give Intermediate N. Intermediate N is reacted with hydrazine to provide Intermediate O. Intermediate O is reacted with dihaloalkanes, such as 1,3-dibromopropane, under basic conditions, for example, in presence of NaH or Cs_2CO_3, to give Intermediate P. Intermediate P, after deprotection of the phenol or thiol, for example, by reacting a methyl protected hydroxy group with BBr_3, can undergo same synthetic sequence as described Scheme 1, Scheme 2,or Scheme 3 to give compound S, which is a compound of Formula (Id). Furthermore, Intermediate W, which is deprotected and subjected to the procedures described and referred to in this paragraph to give compounds of Formula (Id), can be obtained as follows: Intermediate T is reacted under Suzuki conditions in presence of a base and a palladium catalyst with Intermediate U or U', wherein R of Intermediate U or U' is a nitro group or a suitably protected amino group, to give Intermediate V. Intermediate V is subjected to conditions, which reduce the nitro group to an amino group or deprotect the nitrogen to release an amino group, such as zinc in acetic acid or hydrogen and Raney-Nickel, to give Intermediate W.

Scheme 4



4.4 Methods of Use

[00173] Provided herein are methods for the treatment or prevention of pain in a subject in need thereof, wherein the methods comprise administering to the patient in need of such treatment or prevention a Compound provided herein (*i.e.*, a compound of Formula (I), a

compound of Formula (Ia), a compound of Formula (Ib), a compound of Formula (Ic), a compound of Formula (Id), a compound listed in Table 1, or a compound listed in Table 2).

[00174] Provided herein are methods for managing pain comprising administering to a subject in need thereof, a therapeutically effective amount of a Compound, or a pharmaceutically acceptable salt, solvate or tautomeric form thereof.

[00175] Provided herein are methods for treating neuropathic pain comprising administering to a subject in need thereof, a therapeutically effective amount of a Compound, or a pharmaceutically acceptable salt, solvate or tautomeric form thereof.

[00176] Provided herein are methods for treating pain comprising use of a Compound, as a voltage-gated sodium channel inhibitor. In a particular embodiment the methods are those, wherein the pain is neuropathic, nociceptive or inflammatory pain. In a particular embodiment the methods are those, wherein the voltage-gated sodium channel is NaV1.7.

[00177] Provided herein are methods for treating or preventing a NaV1.7-dysfunction-associated disorder comprising administering to a subject in need thereof, a therapeutically effective amount of a Compound, or a pharmaceutically acceptable salt, solvate or tautomeric form thereof.

[00178] Provided herein are methods for prevention or treatment of pain in a subject, wherein the method comprises administering to the subject in need of such prevention or treatment a therapeutically effective amount of a Compound. In a particular embodiment the methods are those, wherein the therapeutically effective amount of a Compound is effective to alleviate pain in a subject, wherein the Compound shows a reduction in pain response in the Formalin Assay (in phase 1 or phase 2, or both) (*see* Section 5.1.2) at a dose between 0.1 mg/kg and 1,000 mg/kg, at a dose between 0.5 mg/kg and 100 mg/kg, at a dose between 1 mg/kg to 50 mg/kg, or at a dose of 5 mg/kg. In certain embodiments, a Compound provided herein shows a reduction in pain response in the Formalin Assay (in phase 1 or phase 2, or both) by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 98%, 99%, or 100%, or by ranges between any of the recited percentages (*e.g.*, 10-20%, 10-30%, 10-40%, 20-30%, or 20-40%) relative to a vehicle control. In a particular embodiment the methods are those, wherein the pain is

nociceptive pain, such as that resulting from physical trauma (e.g., a cut or contusion of the skin; or a chemical or thermal burn), osteoarthritis, rheumatoid arthritis or tendonitis; myofascial pain; neuropathic pain, such as that associated with stroke, diabetic neuropathy, luetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, fibromyalgia, or painful neuropathy induced iatrogenically by drugs; or mixed pain (i.e., pain with both nociceptive and neuropathic components); visceral pain; headache pain (e.g., migraine headache pain); CRPS; CRPS type I; CRPS type II; RSD; reflex neurovascular dystrophy; reflex dystrophy; sympathetically maintained pain syndrome; causalgia; Sudeck atrophy of bone; algoneurodystrophy; shoulder hand syndrome; post-traumatic dystrophy; autonomic dysfunction; autoimmune-related pain; inflammation-related pain; cancer-related pain; phantom limb pain; chronic fatigue syndrome; post-operative pain; spinal cord injury pain; central post-stroke pain; radiculopathy; sensitivity to temperature, light touch or color change to the skin (allodynia); pain from hyperthermic or hypothermic conditions; and other painful conditions (e.g., diabetic neuropathy, luetic neuropathy, postherpetic neuralgia, trigeminal neuralgia); chronic pain; or acute pain.

[00179] Provided herein are methods modulating the activity of a voltage-gated sodium channel, wherein the method comprises contacting a cell that expresses the voltage-gated sodium channel with a Compound. In a particular embodiments the methods are those, wherein the voltage-gated sodium channel is NaV1.7. In a particular embodiments the methods are those, wherein the method results in inhibition of the voltage-gated sodium channel.

[00180] In certain embodiments, a Compound provided herein, is administered to a patient population with a gain of function mutation in a gene encoding the alpha subunit of a voltage gated sodium ion channel, such as NaV1.7.

[00181] In certain embodiments, a Compound provided herein is administered to a patient population diagnosed with erythromelalgia, primary erythromelalgia, paroxysmal extreme pain disorder (PEPD), or NaV1.7-associated fibromyalgia.

4.5 Pharmaceutical Compositions and Routes of Administration

[00182] Provided herein are pharmaceutical compositions comprising a Compound provided herein and a pharmaceutically acceptable carrier. In a particular embodiment the

pharmaceutical compositions are those, wherein the composition is suitable for topical, oral, subcutaneous, or intravenous administration.

[00183] Provided herein are compositions comprising an effective amount of a Compound and compositions comprising an effective amount of a Compound and a pharmaceutically acceptable carrier or vehicle. In some embodiments, the pharmaceutical composition described herein are suitable for oral, parenteral, mucosal, transdermal or topical administration.

[00184] The Compounds can be administered to a patient orally or parenterally in the conventional form of preparations, such as capsules, microcapsules, tablets, granules, powder, troches, pills, suppositories, injections, suspensions and syrups. Suitable formulations can be prepared by methods commonly employed using conventional, organic or inorganic additives, such as an excipient (*e.g.,* sucrose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate or calcium carbonate), a binder (*e.g.,* cellulose, methylcellulose, hydroxymethylcellulose, polypropylpyrrolidone, polyvinylpyrrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose or starch), a disintegrator (*e.g.,* starch, carboxymethylcellulose, hydroxypropylstarch, low substituted hydroxypropylcellulose, sodium bicarbonate, calcium phosphate or calcium citrate), a lubricant (*e.g.,* magnesium stearate, light anhydrous silicic acid, talc or sodium lauryl sulfate), a flavoring agent (*e.g.,* citric acid, menthol, glycine or orange powder), a preservative (*e.g.,* sodium benzoate, sodium bisulfite, methylparaben or propylparaben), a stabilizer (*e.g.,* citric acid, sodium citrate or acetic acid), a suspending agent (*e.g.,* methylcellulose, polyvinyl pyrroliclone or aluminum stearate), a dispersing agent (*e.g.,* hydroxypropylmethylcellulose), a diluent (*e.g.,* water), and base wax (*e.g.,* cocoa butter, white petrolatum or polyethylene glycol). The effective amount of the Compound in the pharmaceutical composition may be at a level that will exercise the desired effect; for example, about 0.1 mg/kg to about 1000 mg/kg or about 0.5mg/kg to about 100mg/kg of a patient's body weight in unit dosage for both oral and parenteral administration.

[00185] The dose of a Compound to be administered to a patient is rather widely variable and can be the judgment of a health-care practitioner. In general, the Compounds can be administered one to four times a day in a dose of about 0.1 mg/kg of a patient's body weight to about 1000 mg/kg of a patient's body weight in a patient, but the above dosage may be properly

varied depending on the age, body weight and medical condition of the patient and the type of administration. In one embodiment, the dose is about 0.05 mg/kg of a patient's body weight to about 500 mg/kg of a patient's body weight, 0.05 mg/kg of a patient's body weight to about 100 mg/kg of a patient's body weight, about 0.5 mg/kg of a patient's body weight to about 100 mg/kg of a patient's body weight, about 0.1 mg/kg of a patient's body weight to about 50 mg/kg of a patient's body weight or about 0.1 mg/kg of a patient's body weight to about 25 mg/kg of a patient's body weight. In one embodiment, one dose is given per day. In another embodiment, two doses are given per day. In any given case, the amount of the Compound administered will depend on such factors as the solubility of the active component, the formulation used and the route of administration.

[00186] In another embodiment, provided herein are methods for the treatment of pain comprising the administration of about 7.5 mg/day to about 75 g/day, about 3.75 mg/day to about 37.5 g/day, about 3.75 mg/day to about 7.5 g/day, about 37.5 mg/day to about 7.5 g/day, about 7.5 mg/day to about 3.75 g/day, about 3.75 mg/day to about 1.875 g/day, about 3.75 mg/day to about 1,000 mg/day, about 3.75 mg/day to about 800 mg/day, about 3.75 mg/day to about 500 mg/day, about 3.75 mg/day to about 300 mg/day, or about 3.75 mg/day to about 150 mg/day of a Compound to a patient in need thereof. In a particular embodiment, the methods disclosed herein comprise the administration of 1 mg/day, 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 45 mg/day, 50 mg/day, 60 mg/day, 75 mg/day, 100 mg/day, 125 mg/day, 150 mg/day, 200 mg/day, 250 mg/day, 300 mg/day, 400 mg/day, 600 mg/day, 800 mg/day, 1,000 mg/day, 1,500 mg/day, 2,000 mg/day, 2,500 mg/day, 5,000 mg/day, or 7,500 mg/day of a Compound to a patient in need thereof.

[00187] In another embodiment, provided herein are unit dosage formulations that comprise between about 7.5 mg to about 75 g, about 3.75 mg to about 37.5 g, about 3.75 mg to about 7.5 g, about 37.5 mg to about 7.5 g, about 7.5 mg to about 3.75 g, about 3.75 mg to about 1.875 g, about 3.75 mg to about 1,000 mg, about 3.75 mg to about 800 mg, about 3.75 mg to about 500 mg, about 3.75 mg to about 300 mg, or about 3.75 mg to about 150 mg of a Compound.

[00188] In a particular embodiment, provided herein are unit dosage formulation comprising about 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 45 mg, 50 mg, 60 mg, 75 mg, 100 mg, 125 mg, 150 mg, 200 mg, 250 mg, 300 mg, 400 mg, 600 mg, 800 mg 1,000 mg, 1,500 mg, 2,000 mg, 2,500 mg, 5,000 mg, or 7,500 mg of a Compound.

[00189] In another embodiment, provided herein are unit dosage formulations that comprise a Compound dosage that achieves a target plasma concentration of the Compound in a patient or an animal model. In a particular embodiment, provided herein are unit dosage formulations that achieves a plasma concentration of the Compound ranging from approximately 0.001 μg/mL to approximately 100 mg/mL, approximately 0.01 μg/mL to approximately 100 mg/mL, approximately 0.01 μg/mL to approximately 10 mg/mL, approximately 0.1 μg/mL to approximately 10 mg/mL, approximately 0.1 μg/mL to approximately 500 μg/mL, approximately 0.1 μg/mL to approximately 500 μg/mL, approximately 0.1 μg/mL to approximately 100 μg/mL, or approximately 0.5 μg/mL to approximately 10 μg/mL in a patient or an animal model. To achieve such plasma concentrations, a Compound or a pharmaceutical composition thereof may be administered at doses that vary from 0.001 μg to 100,000 mg, depending upon the route of administration. In certain embodiments, subsequent doses of a Compound may be adjusted accordingly based on the plasma concentrations of the Compound achieved with initial doses of the Compound or pharmaceutical composition thereof administered to the subject.

[00190] A Compound can be administered once, twice, three, four or more times daily.

[00191] A Compound can be administered orally for reasons of convenience. In one embodiment, when administered orally, a Compound is administered with a meal and water. In another embodiment, the Compound is dispersed in water or juice (*e.g.*, apple juice or orange juice) and administered orally as a suspension. In another embodiment, when administered orally, a Compound is administered in a fasted state.

[00192] The Compound can also be administered intradermally, intramuscularly, intraperitoneally, percutaneously, intravenously, subcutaneously, intranasally, epidurally, sublingually, intracerebrally, intravaginally, transdermally, rectally, mucosally, by inhalation, or topically to the ears, nose, eyes, or skin. The mode of administration is left to the discretion of the health-care practitioner, and can depend in-part upon the site of the medical condition.

[00193] In one embodiment, provided herein are capsules containing a Compound without an additional carrier, excipient or vehicle.

[00194] In another embodiment, provided herein are compositions comprising an effective amount of a Compound and a pharmaceutically acceptable carrier or vehicle, wherein a pharmaceutically acceptable carrier or vehicle can comprise an excipient, diluent, or a mixture thereof. In one embodiment, the composition is a pharmaceutical composition.

[00195] The compositions can be in the form of tablets, chewable tablets, capsules, solutions, parenteral solutions, troches, suppositories and suspensions and the like. Compositions can be formulated to contain a daily dose, or a convenient fraction of a daily dose, in a dosage unit, which may be a single tablet or capsule or convenient volume of a liquid. In one embodiment, the solutions are prepared from water-soluble salts. In general, all of the compositions are prepared according to known methods in pharmaceutical chemistry. Capsules can be prepared by mixing a Compound with a suitable carrier or diluent and filling the proper amount of the mixture in capsules. The usual carriers and diluents include, but are not limited to, inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

[00196] Tablets can be prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. In one embodiment, the pharmaceutical composition is lactose-free. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

[00197] A lubricant might be necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant can be chosen from such slippery solids as talc,

magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils. Tablet disintegrators are substances that swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algins and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethyl cellulose, for example, can be used as well as sodium lauryl sulfate. Tablets can be coated with sugar as a flavor and sealant, or with film-forming protecting agents to modify the dissolution properties of the tablet. The compositions can also be formulated as chewable tablets, for example, by using substances such as mannitol in the formulation.

[00198] When it is desired to administer a Compound as a suppository, typical bases can be used. Cocoa butter is a traditional suppository base, which can be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use.

[00199] The effect of the Compound can be delayed or prolonged by proper formulation. For example, a slowly soluble pellet of the Compound can be prepared and incorporated in a tablet or capsule, or as a slow-release implantable device. The technique also includes making pellets of several different dissolution rates and filling capsules with a mixture of the pellets. Tablets, capsules, or pellets can be coated with a film that resists dissolution for a predictable period of time (the coating may comprise, for example, polymethylacrylates or ethyl cellulose). Even the parenteral preparations can be made long-acting, by dissolving or suspending the Compound in oily or emulsified vehicles that allow it to disperse slowly in the serum.

5 EXAMPLES

5.1 Biological Examples

5.1.1 *In Vitro* Assays

[00200] **Recombinant NaV Cell Lines**

[00201] In vitro assays were performed in recombinant cell line that stably express a heterotrimeric protein of interest from an introduced nucleic acid encoding the alpha subunit (hNav1.7, SCN9A), the beta subunit (SCNB1) and the beta subunit (SCNB2). The cell line was

constructed in Human Embryonic Kidney 293 cells. Additional cell lines stably expressing recombinant Nav1.7 or Nav1.5 alpha subunit alone or in combination with various beta subunits can also be used in *in-vitro* assays.

[00202] To make cells and cell lines provided herein, one can use, for example, the technology described in U.S. Patent 6,692,965 and WO/2005/079462. Both of these documents are incorporated herein by reference in their entirety. This technology provides real-time assessment of millions of cells such that any desired number of clones (from hundreds to thousands of clones) expressing the desired gene(s) can be selected. Using cell sorting techniques, such as flow cytometric cell sorting (*e.g.*, with a FACS machine) or magnetic cell sorting (*e.g.*, with a MACS machine), one cell per well is automatically deposited with high statistical confidence in a culture vessel (such as a 96 well culture plate). The speed and automation of the technology allows multigene recombinant cell lines to be readily isolated.

[00203] **FDSS Membrane Potential *In-Vitro* Assay**

[00204] Membrane potential dye(s): Blue membrane potential dye (Molecular Devices Inc.), or membrane potential-sensitive dye, HLB021-152 (AnaSpec) combined with a fluorescence quencher e.g. Dipicrylamine (DPA), Acid Violet 17 (AV 17), Diazine Black (DB), HLB30818, FD and C Black Shade, Trypan Blue, Bromophenol Blue, HLB30701, HLB30702, HLB30703, Nitrazine Yellow, Nitro Red, DABCYL (Molecular Probes), FD and C Red NO. 40, QSY (Molecular Probes), metal ion quenchers (*e.g.*, Co^{2+}, Ni^{2+}, Cu^{2+}), and iodide ion.

[00205] Assay agonists: Veratridine and scorpion venom proteins modulate the activity of voltage-gated sodium channels through a combination of mechanisms, including an alteration of the inactivation kinetics.

[00206] The resulting activation of sodium channels in stable NaV1.7-expressing cells changes cell membrane potential and the fluorescent signal increases as a result of depolarization.

[00207] Veratridine and scorpion venom from Leiurus quinquestriatus quinquestriatus can be purchased from Sigma-Aldrich (St. Louis, MO). Stock solutions were prepared as 10mM

(veratridine) in DMSO and as 1mg/ml (scorpion venom) in de-ionised water. The sodium channels agonists were diluted in assay buffer to a 4x concentration with final concentration being 2-25 μM for veratridine and 2-20 μg/ml for scorpion venom.

[00208] Test compounds were prepared as 2 - 10mM stock in DMSO. The stock solutions were further diluted in DMSO in serial dilution steps and then transferred to assay buffer as 4x of the final assay concentrations. Test compounds were added during the first addition (pre-stimulation) step in the kinetic read. All test compound concentrations were evaluated in triplicate.

[00209] Cells stably expressing NaV1.7 α, β1 and β2 subunits were maintained under standard cell culture conditions in Dulbecco's Modified Eagles medium supplemented with 10% fetal bovine serum, glutamine and HEPES. On the day before assay, the cells were harvested from stock plates using cell dissociation reagent, *e.g.*, trypsin, CDB (GIBCO) or cell-stripper (Mediatech), and plated at 10,000 - 25,000 cells per well in 384 well plates in growth media. The assay plates were maintained in a 37°C cell culture incubator under 5% CO_2 for 22-48 hours. The media was then removed from the assay plates and membrane potential fluorescent dye diluted in load buffer (137 mM NaCl, 5 mM KCl, 1.25 mM $CaCl_2$, 25 mM HEPES, 10 mM glucose) was added. The cells were incubated with the membrane potential dye for 45-60 mins at 37°C. The dye-loaded assay plates were then placed in the high-throughput fluorescent plate reader (Hamamatsu FDSS). The kinetic read was started with assay plate imaging every second. After 10 s, the assay buffer alone, or test compound diluted in the assay buffer, were added to the cells (1st addition step) and the kinetic read continued every 2 s for 2 mins total after which cells were stimulated with veratridine and scorpion venom (2nd addition step) diluted in assay buffer to evaluate the effects of the test compounds.

[00210] Control response elicited by veratridine and scorpion venom with buffer only (without test compounds added) was taken as the maximal response. Assay results are expressed in relative fluorescence units (RFU) and can be determined by using the maximum signal during the 2nd addition/stimulation step or by computing the difference of maximum and minimum signal during the 2nd addition/stimulation step. The signal inhibition was estimated for each test

compound concentration in triplicate. The data were analyzed using GraphPad Prism 5.01 software to determine the IC50 value for the test compound.

[00211] Examples 1, 2, 3, 12, 13, 16, 26, 32 showed IC50 values less than 0.13 μM; examples 4, 5, 6, 7, 8, 9, 10, 15, 18, 20, and 28 showed IC50 value between 0.13 and 1.0 μM; examples 14, 17, 19, 21, 22, and 23 showed IC50 values greater than 1.0 μM and 20.0 μM.

[00212] **Patchliner Electrophysiological *In-Vitro* Assay**

[00213] The recording of sodium current from stable HEK293 cell lines expressing NaV1.7 or NaV1.5 was done on a Patchliner® instrument, Nanion Technologies. The Patchliner® is a fully automated bench-top patch clamp platform and can record simultaneously from up to eight single cells with GΩ seals.

[00214] For patch-clamp experiments, cells were grown under standard culturing conditions in Dulbecco's Modified Eagles medium supplemented with 10% fetal bovine serum, glutamine and HEPES. Cells were harvested and kept in suspension for up to 4 hours with no significant change in quality or ability to patch. Whole cell patch clamp recordings were conducted according to Nanion's standard procedure for the Patchliner®. Experiments were conducted at room temperature.

[00215] Voltage protocols were designed to establish: 1) peak current amplitude (Imax), 2) test potential (Vmax) and 3) half-inactivation potential (V1/2) for each of the eight individual cells. To determine V1/2, a standard steady-state inactivation protocol was executed using a series of fifteen 500 ms depolarizing pre-pulses in 10 mV increments (starting at -130mV) and immediately followed by a 10 ms test pulse to Vmax. To estimate test compound affinity to the inactivated state of sodium channel (Ki), the holding potential for each cell was set automatically to the V1/2 calculated from a steady-state inactivation data. The current was activated with the following voltage protocol: holding at V1/2 for 2-5 seconds, return to the -120mV for 5-10ms to relieve fast inactivation, stepping to test potential (Vmax) for 10-20 ms. This voltage protocol was repeated every 10 seconds to establish the baseline with 2-3 buffer additions followed by the test compound addition. The dose-dependent inhibition was analyzed using Nanion's Data Analysis Package.

[00216] Examples 1, 2, 5, 6, 8, 11, 12, 13, 15, 16, 20, 24, 26, 28, 29 and 32 showed IC50 values less than 0.1 μM; examples 14, 17, 18, 19, 21, 22, 23, 25 and 33 showed IC50 value between 0.1 and 1.0 μM.

[00217] ***In-vitro* Cytochrome P450 (CYP450) assay for measuring drug metabolism**

[00218] We evaluated interaction of drug candidates with cytochrome P450 enzymes which are a major determinant of drug clearance via oxidative metabolism using a high throughput compatible, fluorescence based CYP450 screening assay (Vivid® CYP450, Invitrogen) according to manufacturer's directions. In brief, test compounds at four different concentrations (μM- 6.0, 2.0, 0.7, 0.2), a positive control (Ketoconazole) and a solvent control were incubated at room temperature in unique wells of a 96-well microtiter plate with CYP3A4 enzyme complex for 20 minutes. A pre-read fluorescence (Ex- 485 nm / Em- 530 nm) was measured at the start of the incubation using a Tecan Safire^2 microplate reader-monochromator to determine background fluorescence. At the end of the incubation period, enzyme substrate and co-enzyme were added and the reaction was kinetically monitored for 1 hour by measuring fluorescence every minute. Effect of test compounds on inhibition of CYP3A4 metabolism of provided substrate was determined by calculating the ratio of the effective reaction rate in presence of test compound to that in the absence of inhibitor.

[00219] Examples 9, 11, 13, 14, 15, 17, 18, 19, 21, and 22 showed 0-25% CYP3A4 inhibition at 6 μM test concentration; examples 5, 6, 8, 10 and 16 showed 25-50% CYP3A4 inhibition at 6 μM test concentration ; examples 1, 2, 3, 4, 12, 20 and 32 showed 50-100% CYP3A4 inhibition at 6 μM test concentration.

5.1.2 *In Vivo* Assays

[00220] **Method for Formalin Test**

[00221] The Formalin Test (pain behaviors) produces two phases of response, phase 1 (0 to 10 minutes post-formalin injection) is related to direct damage on nociceptors at the sensory nerve endings and mimics post-surgical pain and wound pain, while phase 2 (11 to 40 minutes post-formalin injection) is related to neuro- inflammation pain which mimics inflammatory arthritis (joint pain).

[00222] Each animal is acclimatized for 2-3 days prior to tests. Following acclimatization, a test compound, a positive control, such as mexiletine or lidocaine, which are well-known to inhibit pain, or a vehicle control, such as saline, is administered by intraperitoneal injection or oral gavage 15-20 minutes prior to administration of formalin. The time of administration of test compound is recorded. Formalin solution (1.25%) in PBS is injected subcutaneously (s.c) in a volume of 50 μL into the dorsum of a hindpaw of each rat at time (T)=0 minutes. Each animal is then placed in a clear observation chamber. Observation is started at T= 1 minute to 60 minutes post-injection. The number of flinches (licking, biting, or shaking) per minute is recorded for each animal by an automated nociception analyzer. This is accomplished by measuring the movement of a small metal band (0.5 grams) that is placed on the ankle near the injected paw 15-30 minutes before administration of the test compound. Formalin is injected into the paw with the band and the animal is then placed without restraint inside the observation chamber over an electromagnetic detector system. The paw flinches are detected by the system and counted automatically using a computer. At the end of the test, a file is written that contains identifying information for each animal and the number of flinches per minute over time. The Foot fault test is conducted 75 minutes post-dosing. Other observations of changes in movement such as immobility and seizure are recorded during the whole study period. At the end of study, the animals are euthanized.

[00223] Examples 1, 2, 6, 8 and 12 showed reduction in pain response of 24-78% (formalin assay, phase 1) and 29-73% (formalin assay phase 2) relative to vehicle control at doses of 3 to 30 mg/kg via the intraperitoneal route.

[00224] Example 1 showed reduction in pain response of 14% (formalin assay, phase 1) and 17% (formalin assay phase 2) relative to vehicle control at a dose of 75 mg/kg via the oral route.

[00225] Example 12 showed reduction in pain response of 13-24% (formalin assay, phase 1) and 29-43% (formalin assay phase 2) relative to vehicle control at a dose of 150μL of 1 or 2% w/v solution via the topical route.

[00226] **Method Of Partial Sciatic Nerve Ligation (PSNL)**

[00227] The Partial Sciatic Nerve Ligation Model is associated with neuropathic pain such as spinal disc bulge and diabetic nerve damage.

[00228] 250-350g male Sprague-Dawley rats from appropriate animal resources are anesthetized with 2.5% isoflurane. A hind leg is shaved, and the skin is sterilized with 0.5% iodine and 75% alcohol. All surgical instruments are sterilized before surgery and between animals. An incision (1 cm) is made at the middle of the thigh in parallel with the muscle and sciatic nerve distribution. The muscle is exposed and dissected at the joint of two muscles (biceps femoris) indicated by the light colored (white) fascia line. The sciatic nerve is just beneath the muscle and is hooked out using an 18-20G feeding needle (90 degree curved); the sciatic nerve is flat on the feeding needle and approximately one-half the diameter of the nerve is tightly ligated with 7-0 silk suture. A response of the injured leg twitch indicates the success of ligation. After checking hemostasis, bupivicaine 0.1-0.2 ml (0.125%) is given at the incision area, the muscle and the adjacent fascia are closed with 5-0 absorbable sutures. The skin is sutured with absorbable suture and tissue glue. Sham surgery animals (about 8-10 animals) undergo the same surgical procedure but with no ligation. Animals are returned to their home cage after recovery from anesthesia.

[00229] The following behavioral tests were conducted started on day 3 and thereafter once weekly following surgery.

[00230] **Thermal Hyperalgesia:**

[00231] The plantar test quantitatively assesses the thermal threshold of the hindpaw. Rats are placed on the glass surface of a thermal testing apparatus (Model 336, IITC/Life Science Instruments, Woodland Hills, CA) and are allowed to acclimate for 10 min before testing on the glass surface at room temperature. The animals are placed in chambers with the temperature of the glass surface maintained constant at 30-32°C. A mobile radiant heat source located under the glass is focused onto the hindpaw of each rat. The device is set at 55% (heating rate ~ 3°C per sec) heating intensity with a cut-off at 10 sec. The paw withdrawal latency was recorded by a digital timer. The thermal threshold is determined as the mean withdrawal latency from two to

three consecutive trials of both hindpaws The cutoff of 10 s was used to prevent potential tissue damage.

[00232] **Mechanical Hyperalgesia**

[00233] The paw pressure test assesses nociceptive mechanical thresholds, expressed in grams, and is measured with a Ugo Basil Analgesimeter (Varese, Italy). The test is performed by applying a noxious (painful) pressure to the hindpaw. By pressing a pedal that activates a motor, the force is increased (32 g/s) on a linear scale. When the animal displays pain by withdrawal of the paw or vocalization, the pedal is immediately released and the nociceptive pain threshold read on a scale (a cutoff of 150 g is used to avoid tissue injury) (Courteix *et al.* 1994). Both hindpaws are used for assessment of mechanical hyperalgesia. At least two trials, separated by 10 min, are performed in each rat, and the mean value is used. A testing session for a particular rat begins after 5 min of habituation or as soon as the rat stops exploring and appears acclimatized to the testing environment.

[00234] **Tactile Allodynia**

[00235] The Von Frey test quantifies mechanical sensitivity of the hindpaw, The test utilizes a non-noxious stimulus, and is therefore considered to measure tactile allodynia. Animals are placed under clear plastic boxes above a wire mesh floor, which allowed full access to the paws. Behavioral acclimation is allowed for at least 5 min. Mechanical paw withdrawal thresholds (PWTs) are measured with the up–down testing paradigm. Von Frey filaments in log increments of force (2.0, 4.0, 6.0, 8.0, 10.0, 15.0, 26, 60 g or size 4.31, 4.56, 4.74, 4.93, 5.07, 5.18, 5.46, 5.88) are applied for a duration of 2-3 s to the mid–plantar paw in neuropathic pain (i.e. PSNL) animals. Application is to the central region of the plantar surface avoiding the foot pads. The 4.0-g stimulus is applied first. Whenever a withdrawal response to a given probe occurs, the next smaller von Frey probe is applied. Whenever a negative response occurs, the next higher von Frey probe is applied. The test continued until (1) the responses of four more stimuli (total 3-5 trials) after the first change in response has been obtained or (2) the upper/lower end of the von Frey hair is reached (bending). If the animal shows no response to any of the von Frey hairs, a value of 26 g, corresponding to the next log increment in potential von Frey filament, is assigned as the threshold. The testing is continued until the hair with the

lowest force to induce a rapid flicking of paw is determined or when the cut off force of approximately 26 g is reached. This cut off force is used because it represent approximately 10% of the animals' body weight and serves to prevent rising of the entire limb due to the use of stiffer hairs, which would change the nature of the stimulus. The value of each hair is confirmed weekly by measuring the magnitude in grams exerted by the hair when applied to an electronic balance. The hair is applied only when the rat is stationary and standing on all four paws. A withdrawal response is considered valid only if the hind paw is completely removed from the platform. Although infrequent, if a rat walks immediately after application of a hair instead of simply lifting the paw, the hair is reapplied. On rare occasions, the hind paw only flinches after a single application; as the hind paw is not lifted from the platform, this is not considered a withdrawal response. A trial consists of application of a von Frey hair to the hind paw five times at 5 s intervals or as soon as the hind paw is placed appropriately on the platform. If withdrawal does not occur during five applications of a particular hair, the next larger hair in the series is applied in a similar manner. When the hind paw is withdrawn from a particular hair either four or five times out of the five applications, the value of that hair in grams is considered to be the withdrawal threshold. Once the threshold is determined for the left hind paw, the same testing procedure is repeated on the right hind paw after 5 min.

[00236] **Weight Bearing**

[00237] Rats are tested for hypersensitivity and spontaneous pain in the weight-bearing test, using an Incapacitance tester (Linton Instruments, Norfolk, UK). The rat is placed into the plastic box of the device. The integrated paw pressure during this period (1-2 seconds) is displayed separately for the right and left leg. The ratio between the pressure of the right and left leg is calculated as left/right hind leg weight distribution ratio. The weight bearing assay is repeated 3 times in 5 minutes. The mean distribution ratio of 3 assays is calculated.

[00238] Examples 1 and 2 showed recovery of pain response of 49-62% (paw pressure test), 59-73% (plantar test) and 50-66% (weight bearing) relative to vehicle control at a dose of 30 mg/kg via the intraperitoneal route.

[00239] **Writhing Model**

[00240] The Acetic Acid Writhing Model is associated with visceral pain (abdominal pain, such as stomach pain, and pain caused by, for example, bile duct congestion and kidney stones).

[00241] A writhing test assesses acute peritoneovisceral pain. After acclimation of 2-3 days, a test compound, positive control or vehicle control is administered by intraperitoneal injection (i.p.) or by oral gavage 15-30 minutes prior to administration of acetic acid. The time of administration of test compound is recorded. For mice: 0.6% Acetic acid solution in saline is injected i.p in a volume of 10 ml/kg. For rats: 4% acetic acid in saline is injected i.p in a volume of 2 ml/kg at T= 0 minutes. Each animal is placed in a clear plastic cage. At T = 5 minutes, the number of writhing movements is counted over a 45 minute period. Alternatively, the writhing movements are counted over a 5- minute period and repeated every 5 minutes, starting at T=5 minutes over a 45- minute period.

[00242] Example 2 showed reduction in pain response of 48-58% relative to vehicle control at doses of 10 to 30 mg/kg via the intraperitoneal route.

5.2 Examples of NaV Modulators

5.2.1 General Methods

5.2.1.1 LCMS Method

[00243] Method-A

[00244] LC-MS was carried out on Acquity H-Class UPLC, PDA and SQ Detector. The column used was BEH C18 50 X 2.1 mm, 1.7 micron and column flow was 0.55 ml /min. Mobile phase were used (A) 0.1 % Formic acid + 5mM Ammonium Acetate in water and (B) 0.1 % Formic acid in Acetonitrile. The UV spectra were recorded at its lambda Max and Mass spectra were recorded using ESI technique. The following gradient is used to monitor reaction progress and analyze final products.

Time (min)	%A	%B
0.01	95	05
0.40	95	05
0.80	65	35
1.20	45	55
2.50	00	100
3.30	00	100
3.31	95	05
4.00	95	05

[00245] Method-B

[00246] LC-MS was carried out on Waters LC alliance 2995, PDA 2996 and SQ Detector. The column used was X-BRIDGE C18 150 X 4.6 mm X5 micron and column flow was 1.0 ml /min. Mobile phase were used (A) 0.1 % Ammonia in water and (B) 0.1 % Ammonia in Acetonitrile. The UV spectra were recorded at its lambda Max and Mass spectra were recorded using ESI technique. The following gradient is used to monitor reaction progress and analyze final products.

Time (min)	%A	%B
0.01	90	10
5.00	10	90
7.00	00	100
11.00	00	100
11.01	90	10
12.00	90	10

[00247] Method-C

[00248] LC-MS was carried out on Waters LC alliance 2995, PDA 2996 and SQ Detector. The column used was X-BRIDGE C18 150 X 4.6 mm X5 micron and column flow was 1.0 ml/min. Mobile phase were used (A) 0.1 % Ammonia in water and (B) 0.1 % Ammonia in Acetonitrile. The UV spectra were recorded at its lambda Max and Mass spectra were recorded using ESI technique. The following gradient is used to monitor reaction progress and analyze final products.

Time (min)	%A	%B
0.01	100	00
7.00	50	50
9.00	00	100
11.00	00	100
11.01	100	00
12.00	100	00

[00249] Method-D

[00250] LC-MS was carried out on Waters LC alliance 2995, PDA 2996 and SQ Detector. The column used was X-BRIDGE C18 150 X 4.6 mm X5 micron and column flow was 1.0 ml/min. Mobile phase were used (A) 20mM Ammonium Acetate in water and (B) 100% Methanol. The UV spectra were recorded at its lambda Max and Mass spectra were recorded using ESI technique. The following gradient is used to monitor reaction progress and analyze final products.

Time (min)	%A	%B
0.01	90	10
5.00	10	90
7.00	00	100
11.00	00	100
11.01	90	10
12.00	90	10

5.2.1.2 HPLC Method

[00251] Method-A

[00252] HPLC was carried out on Waters e2695, PDA Detector. The column used was Phenomenex Gemini, C18 150 X 4.6 mm, 5 micron and column flow was 1.00 ml /min. Mobile phase were used (A) 0.1 % Formic acid in water and (B) 0.1 % Formic acid in Acetonitrile. The UV spectra were recorded at its lambda Max. The following gradient is used.

Time (min)	%A	%B
0.01	90	10
7.00	10	90
9.00	00	100
13.00	00	100
13.01	90	10
17.00	90	10

[00253] Method-B

[00254] HPLC was carried out on Waters e2695, PDA Detector. The column used was Phenomenex Gemini, C18 150 X 4.6 mm, 5 micron and column flow was 1.00 ml/min. Mobile phase were used (A) 0.1 % Formic acid in water and (B) 0.1 % Formic acid in Acetonitrile. The UV spectra were recorded at its lambda Max. The following gradient is used.

Time (min)	%A	%B
0.01	100	00
7.00	50	50
9.00	00	100
13.00	00	100
13.01	100	00
17.00	100	00

[00255] Method-C

[00256] HPLC was carried out on Waters e2695, PDA Detector. The column used was X-BRIDGE, C18 150 X 4.6 mm, 5 micron and column flow was 1.00 ml/min. Mobile phase were used (A) 0.1 % Ammonia in water and (B) 0.1 % Ammonia in Acetonitrile. The UV spectra were recorded at its lambda Max. The following gradient is used.

Time (min)	%A	%B
0.01	90	10
7.00	10	90
9.00	00	100
13.00	00	100
13.01	90	10
17.00	90	10

[00257] Method-D

[00258] HPLC was carried out on Waters e2695, PDA Detector. The column used was X-BRIDGE, C18 150 X 4.6 mm, 5 micron and column flow was 1.00 ml/min. Mobile phase were used (A) 0.1 % Ammonia in water and (B) 0.1 % Ammonia in Acetonitrile. The UV spectra were recorded at its lambda Max. The following gradient is used.

Time (min)	%A	%B
0.01	100	00
7.00	50	50
9.00	00	100
13.00	00	100
13.01	100	00
17.00	100	00

5.2.1.3 PREP HPLC Method

[00259] Method-A

[00260] PREP HPLC was carried out on Shimadzu UFLC, LC-20 AP, and UV Detector. The column used was Sunfire OBD, C18 250 X 19 mm, 5 micron and column flow was 18.00 ml /min. Mobile phase were used (A) 0.1 % HCL in water and (B) 100% Acetonitrile. The UV spectra were recorded at its lambda Max. The following gradient was used.

Time (min)	%A	%B
0.01	90	10
7.00	10	90
9.00	00	100
13.00	00	100
13.01	90	10
17.00	90	10

[00261] Method-B

[00262] PREP HPLC was carried out on Shimadzu UFLC, LC-20 AP, and UV Detector. The column used was Sunfire OBD, C18 250 X 19 mm, 5 micron and column flow was 18.00 ml /min. Mobile phase were used (A) 0.1 % Formic acid in water and (B) 0.1% Formic acid in

Acetonitrile. The UV spectra were recorded at its lambda Max. The following gradient was used.

Time (min)	%A	%B
0.01	90	10
7.00	10	90
9.00	00	100
13.00	00	100
13.01	90	10
17.00	90	10

[00263] Method-C

[00264] PREP HPLC was carried out on Shimadzu UFLC, LC-20 AP, and UV Detector. The column used was X-BRIDGE, C18 250 X 19 mm, 5 micron and column flow was 18.00 ml /min. Mobile phase were used (A) 0.1 % Ammonia in water and (B) 0.1% Ammonia in Acetonitrile. The UV spectra were recorded at its lambda Max. The following gradient was used.

Time (min)	%A	%B
0.01	90	10
7.00	10	90
9.00	00	100
13.00	00	100
13.01	90	10
17.00	90	10

5.2.1.4 List of Abbreviations

[00265] Ac = Acetyl

[00266] EtOAc = ethyl acetate

[00267] Bn = Benzyl

[00268] Boc = tert-Butoxycarbonyl

[00269] Bzl = Benzyl

[00270] DBU = 1,8-Diazabyciclo[5.4.0]undec-7-ene

[00271] DCC = 1,3-Dicyclohexylcarbodiimide

[00272] DCM = Dichloromethane

[00273] DEAD = Diethyl azodicarboxylate

[00274] DIC = Diisopropylcarbodiimide

[00275] DIPEA = Diisopropylethylamine

[00276] D. M. water = demineralized water

[00277] DME = 1,2-Dimethoxyethane

[00278] DMF = N,N-Dimethylformamide

[00279] DMSO = Dimethylsulphoxide

[00280] EDC = 1-Ethyl-3-(3-dimethylaminopropy)carbodiimide hydrochloride

[00281] Et_2O = Diethyl ether

[00282] HOBt = 1-Hydroxybenzotriazole

[00283] IPA = Isopropyl alcohol

[00284] KHMDS = Potassium bis(trimethylsilyl)amide

[00285] LAH = Lithium aluminium hydride

[00286] LDA = Lithium diisopropylamide

[00287] LHMDS = Lithium bis(trimethylsilyl)amide

[00288] MOM = Methoxymethyl

[00289] NaHMDS = Sodium bis(trimethylsilyl)amide

[00290] NBS = N-Bromosuccinimide

[00291] Ph = Phenyl

[00292] PMB = p-Methoxybenzyl

[00293] Py = Pyridine

[00294] TEA = Triethylamine

[00295] TFA = Trifluoroacetic acid

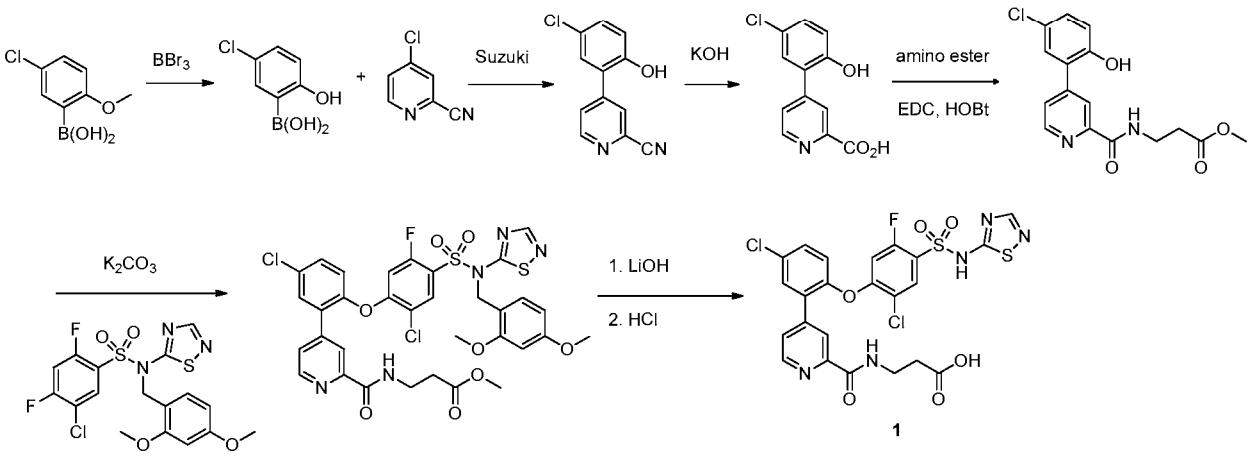
[00296] THF = Tetrahydrofurane

[00297] Tol = p-Toluyl

5.2.2 Examples

Example 1: Synthesis of 3-(4-(2-(4-(N-1,2,4-thiadiazol-5-ylsulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoicacid

Scheme 5



[00298] Step 1: Preparation of (5-chloro-2-hydroxyphenyl)boronic acid.

[00299] A solution of 5-chloro-2-methoxyphenylboronic acid (10.0g, 53.6 mmol) in dichloromethan (100ml) was cooled to temperature between 5-10 °C. To the above mixture, 100ml 1M solution of borontribromide in DCM was added drop wise using a pressure equalizing dropping funnel, over a period of 30 minutes. The resulting reaction mixture was then stirred room temperature for 30 minutes. After completion of reaction, the mixture was poured drop wise on to an ice cold saturated sodium bicarbonate solution (600ml). The resulting mixture was allowed to stir at room temperature for 1 hr. The DCM layer was separated out and the aqueous layer thus collected was cooled to temperature between 10-15 °C. 1N solution of dilute hydrochloric acid was then added to the above cooled aqueous layer and this resulted in precipitate formation. The solid was filtered off under vacuo and dried to afford 9 g (yield: 97%) of product. LC-MS: m/z = 170.9 (M+H).

[00300] Step 2: Preparation of 4-(5-chloro-2-hydroxyphenyl)picolinonitrile

[00301] To a solution of 4-Chloropicolinonitrile (1.0g, 7.2 mmol) in IPA:toluene(7ml:7ml) were sequentially added (5-chloro-2-hydroxyphenyl)boronic acid (1.49g, 8.65 mmol) and potassium carbonate (3.99g, 21.64 mmol) at room temperature. The resulting

reaction mixture was degassed for 15 minutes by purging with nitrogen. Thereafter calculated quantity of Tetrakis (0.416g, 0.36 mmol) was added to the reaction mixture, nitrogen purging was further continued for next 20 minutes. The resulting reaction mixture was then refluxed at 100 °C for 20 hours. After completion of the reaction, the mixture was concentrated under vacuo. To the resulting crude mass water (50ml) was added and the mixture was extracted with ethyl acetate (3 x 25ml). The combined organic extract was washed with water (20ml), brine (20ml), dried over sodium sulfate and concentrated under vacuo to get the desired crude product. The crude product was purified by column chromatography using normal phase silica gel. The desired product eluted at around 20-30% ethyl acetate in hexane. Evaporation of the product fractions gave 0.8g (yield, 48%) of desired product as a solid. LC-MS: m/z = 231.1 (M+H).

[00302] Step 3: Preparation of 4-(5-chloro-2-hydroxyphenyl)picolinic acid)

[00303] To a solution of 4-(5-chloro-2-hydroxyphenyl)picolinonitrile (0.5g, 2.17 mmol) in THF(20ml) was added a solution of potassium hydroxide (4.276g, 14 mmol) in water (10ml) solution at room temperature. The resulting reaction mixture was then refluxed at 100 °C for 5 hours. After completion of the reaction, the mixture was concentrated under vacuo. Ice cold water was added in to the reaction mixture, the resulting mixture was then acidified between pH 3 - 6 with 1N HCl. The resulting solid precipitate was filtered and dried to afford 0.5g (yield, 93%) of product as a solid. LC-MS: m/z = 249.8 (M+H).

[00304] Step 4: Preparation of methyl 3-(4-(5-chloro-2-hydroxyphenyl)-picolinamido)propanoate)

[00305] To a solution of 4-(5-chloro-2-hydroxyphenyl)picolinic acid (0.6g, 2.40 mmol) in THF (20ml) was sequentially added EDC (0.69g, 3.61 mmol) and HOBT (0.49g, 3.61 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes. Beta-alanine methyl ester (0.40g, 2.88mol) was added at 0 °C. The reaction mixture temperature was then allowed to rise to room temperature and stirred for 20 hours. After completion of reaction, water (50 ml) was added in to the reaction mixture. The resulting mixture was then extracted with ethyl acetate (3 x 25ml).The combined organic extract was washed with water (20ml), brine (20ml), dried over sodium sulfate and concentrated under vacuo to get the desired crude product. The crude product was purified by column chromatography using normal phase silica gel. The desired

product eluted at around 0-5% Methanol in dichloromethane. Evaporation of the product fractions gave 0.72g (yield: 89%) of desired product. LC-MS: m/z = 335.6 (M+H).

[00306] Step 5: Synthesis of methyl-3-(4-(5-chloro-2-(2-chloro-4-(N-(2,4-dimethoxybenzyl) -N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-5-fluorophenoxy)phenyl)picolinamido)propanoate)

[00307] To a solution of methyl 3-(4-(5-chloro-2-hydroxyphenyl)picolinamido)propanoate) (0.72g, 2.15 mmol) in DMF (10ml) was added K_2CO_3 (0.59g, 4.3mol) in one portion under nitrogen atmosphere at room temperature. The resulting reaction mixture was then allowed to stir at room temperature for 15 minutes. To the above reaction mixture was then added calculated quantity of 5-chloro-N-(2,4-dimethoxybenzyl)-2,4-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide (1.0g, 2.15mol). The resulting reaction mixture was further allowed to stir at room temperature for 3 hours. After completion of reaction, water (10ml) was added and the resulting mixture was extracted with ethyl acetate (3 x 25ml). The combined organic extract was washed with water (20ml), brine (20ml), dried over sodium sulfate and concentrated under vacuo. The crude product was purified by column chromatography using normal phase silica gel. The desired product eluted at around 20 to 25% ethyl acetate in hexane. Evaporation of the product fractions gave 1.0g (yield: 60%) of desired product. LC-MS: m/z = 776.3 (M+H).

[00308] Step 6: Preparation of 3-(4-(5-chloro-2-(2-chloro-4-(N-(2,4-dimethoxybenzyl) -N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-5-fluorophenoxy)phenyl)picolinamido)propanoic acid)

[00309] To the solution of methyl-3-(4-(5-chloro-2-(2-chloro-4-(N-(2,4-dimethoxybenzyl)-N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-5-fluorophenoxy)phenyl)picolinamido)propanoate) (1.0g, 1.28 mmol) in THF (10mL) was added a solution of Lithium hydroxide monohydrate (0.27g, 6.43 mmol) in water (5ml). The resulting reaction mixture was then allowed to stir at room temperature for 3 hours. After completion of reaction, ice cold water was added in to the reaction mixture, the resulting mixture was acidified between pH 4-6 with 1N HCl. The resulting acidic aqueous was extracted with Ethyl acetate (3 x 25ml). The combined organic extract was washed with water (20ml), brine (20ml), dried over sodium sulphate and concentrated under vacuo. The crude product was purified by column

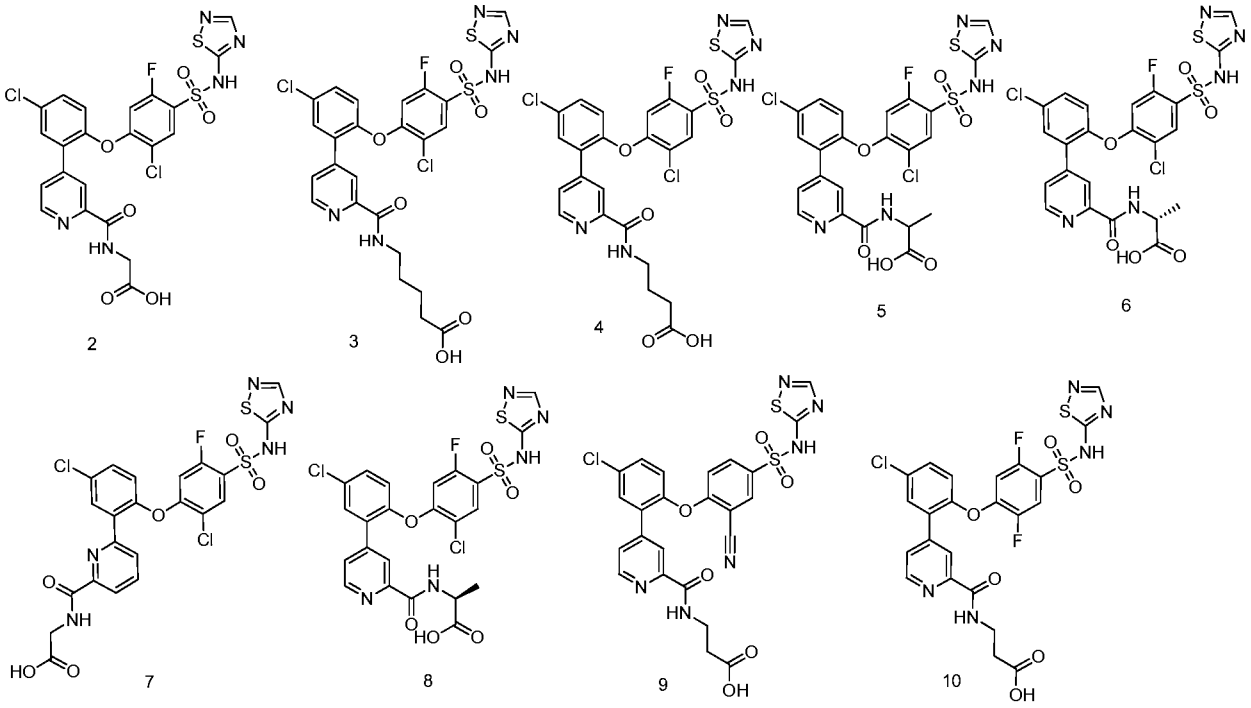
chromatography using normal phase silica gel. The desired product eluted at around 0 to 5% methanol in dichloromethane. Evaporation of the product fractions gave 1g (yield: 99%) of desired product. LC-MS: m/z = 762.8 (M+H).

[00310] Step 7: Preparation of 3-(4-(2-(4-(N-1,2,4-thiadiazol-5-ylsulfamoyl)-2-chloro-5-fluorophenoxy) -5-chlorophenyl)picolinamido)propanoicacid

[00311] To the solution of 3-(4-(5-chloro-2-(2-chloro-4-(N-(2,4-dimethoxybenzyl) -N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-5-fluorophenoxy)phenyl)picolinamido)propanoic acid) (1.0 g, 1.3 mmol) in DCM (10ml) was added drop wise 4N solution of hydrochloric acid in ethyl acetate (0.5ml) at room temperature. The resulting reaction mixture was further stirred at room temperature for 2 hour. After completion of reaction, pentane (20ml) was added in to the reaction mixture which resulted in precipitation of solid. The solid thus obtained was washed twice with pentane (15ml) and dried under vacuo. The resulting crude material was further purified by Prep HPLC using 0.1% HCl in water:acetonitrile mobile phase. Evaporation of the pure Prep fractions gave 0.29g (yield: 34%) of desired product as HCl salt. LC-MS: m/z = 612.9 (M+H). 1H NMR (DMSO-d6), δ 9.03 (br, 1H), 8.71 (d, *J* = 4.8 Hz, 1H), 8.51 (s, 1H), 8.20 (s, 1H), 7.88 (d, *J* = 7.2 Hz, 1H), 7.80 (br, 2H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.22 (d, *J* = 10.8 Hz, 1H), 4.01 (br, 2H).

[00312] The following nine compounds were synthesized according to the synthetic scheme described for example 1.

Scheme 6



Example 2: 2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)acetic acid

[00313] Compound **2** was synthesized according to the procedure described for the synthesis of example **1** by replacing beta-alanine methyl ester with glycine methyl ester hydrochloride in step 4. LC-MS: m/z = 598.5 (M+H). 1H NMR (DMSO-d6), δ 9.03 (t, *J* = 6.0 Hz, 1H), 8.71 (d, *J* = 4.8 Hz, 1H), 8.53 (s, 1H), 8.19 (s, 1H), 7.88 (d, *J* = 7.2 Hz, 1H), 7.78 – 7.81 (m, 2H), 7.60 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.22 (d, *J* = 10.8 Hz, 1H), 4.00 (br, 2H).

Example 3: 5-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)pentanoic acid

[00314] Compound **3** was synthesized according to the procedure described for the synthesis of compound **1** by replacing beta-alanine methyl ester methyl 5-aminopentanoate in step 4. LC-MS: m/z = 640.2 (M+H).

Example 4: 4-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)butanoic acid

[00315] Compound 4 was synthesized according to the procedure described for the synthesis of compound **1** by replacing beta-alanine methyl ester with methyl 4-aminobutanoate in step 4. LC-MS: m/z = 626.6 (M+H). 1H NMR (MeOH-d4), δ 8.65 (d, *J* = 4.8 Hz, 1H), 8.27 (s, 1H), 8.26 (s, 1H), 7.91 (d, *J* = 6.8 Hz, 1H), 7.74 (d, *J* = 4.4 Hz, 1H), 7.71 (d, *J* = 2.4 Hz, 1H), 7.60 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 6.94 (s,1H), 6.78 (d, *J* = 10.8 Hz, 1H), 3.75 (br, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 1.97 (t, *J* = 7.2 Hz, 2H).

Example 5: (*Rac*)-2-(4-(2-(4-(N-1,2,4-thiadiazol-5-ylsulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid

[00316] Compound **5** was synthesized according to the procedure described for the synthesis of compound **1** by replacing beta-alanine methyl ester with DL-alanine methyl ester hydrochloride in step 4. LC-MS: m/z = 613.8 (M+H). 1H NMR (MeOH-d4), δ 8.65 (d, *J* = 5.6 Hz, 1H), 8.27 (s, 1H), 8.25 (s, 1H), 7.90 (d, *J* = 6.8 Hz, 1H), 7.74 (dd, *J* = 1.6, 4.8 Hz, 1H), 7.70 (d, *J* = 2.4 Hz, 1H), 7.59 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 6.78 (d, *J* = 10.8 Hz, 1H), 4.63 (q, *J* = 7.2 Hz, 1H), 1.56 (d, *J* = 7.6 Hz, 3H).

Example 6: (*R*)-2-(4-(2-(4-(N-1,2,4-thiadiazol-5-ylsulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid

[00317] Compound **6** was synthesized according to the procedure described for the synthesis of compound **1** by replacing beta-alanine methyl ester with D-alanine methyl ester hydrochloride in step 4. LC-MS: m/z = 613.8 (M+H). 1H NMR (MeOH-d4), δ 8.67 (d, *J* = 5.2 Hz, 1H), 8.27 (s, 1H), 8.25 (s, 1H), 7.91 (d, *J* = 7.2 Hz, 1H), 7.75 (dd, *J* = 2.0, 5.2 Hz, 1H), 7.71 (d, *J* = 2.8 Hz, 1H), 7.60 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 6.78 (d, *J* = 10.8 Hz, 1H), 4.63 (q, *J* = 7.2 Hz, 1H), 1.56 (d, *J* = 7.6 Hz, 3H).

Example 7: 2-(6-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)acetic acid

[00318] Compound **7** was synthesized according to the procedure described for the synthesis of compound **1** by replacing 4-Chloropicolinonitrile with 6-chloropicolinonitrile in step 2. LC-MS: m/z = 597.7 (M+H). 1H-NMR (MeOD), δ 8.19 (s, 1H), 8.00 – 8.07 (m, 4H), 7.9s (d, J = 6.8 Hz, 1H), 7.59(dd, *J* = 2.4,8.8 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 6.72 (d, J = 10.4 Hz, 1H), 4.09(s, 2H).

Example 8: (*S*)-2-(4-(2-(4-(N-1,2,4-thiadiazol-5-ylsulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid

[00319] Compound **8** was synthesized according to the procedure described for the synthesis of compound **1** by replacing beta-alanine methyl ester with L-alanine methyl ester hydrochloride in step 4. LC-MS: m/z = 612.6 (M+H). 1H NMR (DMSO-d6), δ 8.85 (d, *J* = 7.6 Hz, 1H), 8.71 (d, *J* = 5.6 Hz, 1H), 8.52 (s, 1H), 8.19 (s, 1H), 7.88 (d, *J* = 7.2 Hz, 1H), 7.78 – 7.80 (m, 2H), 7.60 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 1H), 7.22 (d, *J* = 10.8 Hz, 1H), 4.47 (q, *J* = 7.2 Hz, 1H), 1.42 (d, *J* = 7.2 Hz, 3H).

Example 9: 3-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-cyanophenoxy)-5-chlorophenyl)picolinamido)propanoic acid

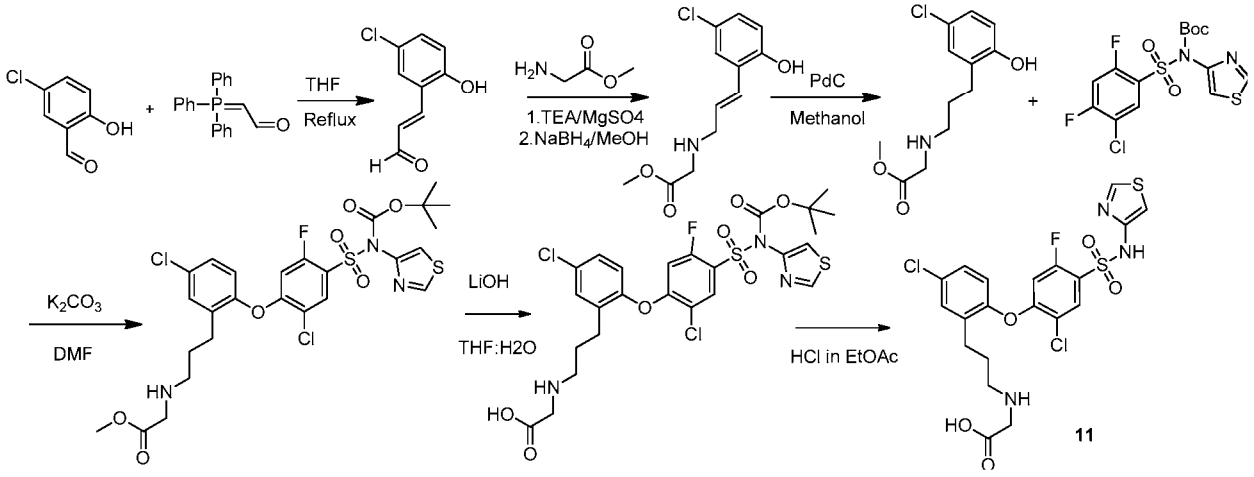
[00320] Compound **9** was synthesized according to the procedure described for the synthesis of compound **1** by replacing 5-chloro-N-(2,4-dimethoxybenzyl)-2,4-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide with 3-cyano-N-(2,4-dimethoxybenzyl)-4-fluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide in step 5. LC-MS: m/z = 584.8 (M+H). 1H-NMR (MeOD), δ 8.63 (d, *J* = 4.8 1H), 8.23 (s, 1H), 8.19 (s,1H), 8.14 (d, *J* = 2.0 Hz, 1H), 7.95 (dd, J = 2.4, 8.8 Hz, 1H), 7.74 – 7.76 (m, 2H), 7.63 (dd, *J* = 2.4,8.8 Hz, 1H), 6.97 (d, *J* = 10.0 Hz, 1H), 3.68(t, *J* = 6.8 Hz, 2H), 2.65 (t, *J* = 6.8 Hz, 2H).

Example 10: 3-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2,5-difluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid

[00321] Compound **10** was synthesized according to the procedure described for the synthesis of compound **1** by replacing 5-chloro-N-(2,4-dimethoxybenzyl)-2,4-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide with N-(2,4-dimethoxybenzyl)-2,4,5-trifluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide in step 5. LC-MS: m/z = 595.8 (M+H). 1H-NMR (MeOD), δ 8.66 (d, *J* = 4.8 1H), 8.28 (s, 1H), 8.26 (s,1H), 7.69 – 7.77 (m, 3H), 7.56 (dd, *J* = 2.8, 8.8 Hz, 1H), 6.94 (dd, *J* = 6.4,10.0 Hz, 1H), 3.70(t, *J* = 6.4 Hz, 2H), 2.67 (t, *J* = 6.8 Hz, 2H).

Example 11: Preparation of 2-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-thiazol-4-ylsulfamoyl)phenoxy)phenyl)propylamino) acetic acid

Scheme 7



[00322] Step 1: Preparation of 3-(5-chloro-2-hydroxyphenyl)acrylaldehyde

[00323] To a solution of 5-chloro-2-hydroxybenzaldehyde (20g, 127mmol) in THF (300ml) was added (formylmethylene)triphenylphosphorane (43g, 140mmol) at room temperature. The resulting reaction mixture was refluxed at 100 °C for 20 hours. The reaction mixture was cooled to room temperature, and extracted with water (200ml) and ethyl acetate (3 x 250ml). The combined organic phase was washed with water (200ml), brine (200ml), dried over sodium sulphate and concentrated under vacuo to give the desired crude product. The crude product was purified by column chromatography using normal phase silica gel. The desired

product eluted at around 20- 30% ethyl acetate in hexane. Evaporation of the product fractions gave 20g (yield, 87%) of desired compound as yellow solid. LC-MS: m/z= 183.4(M+H).

[00324] Step 2: Preparation of methyl 2-(3-(5-chloro-2-hydroxyphenyl) allylamino) acetate

[00325] To a solution of 3-(5-chloro-2-hydroxyphenyl)acrylaldehyde (5g, 27mmol) and glycine methyl ester hydrochloride (4.1g, 32mmol) in dichloromethane (80ml) was added magnesium sulphate (6g, 50mmol) and triethylamine (12ml, 82mmol) at room temperature. The above reaction mixture was stirred at room temperature for 18 hours. The resulting reaction mixture was then concentrated under vacuo. The concentrated mass thus obtained was dissolved in methanol (50ml) and cooled to a temperature between 5-10 °C. To the above mixture, sodium borohydride (3.0g, 82mmol) was added in small portions over a period of 20 minutes; during addition temperature of the reaction mixture was maintained between 10 - 20 °C. The reaction mixture was allowed to stir at room temperature for 2 hours and concentrated under vacuum. Water (100ml) was added to the above crude mass and the resulting mixture was extracted with ethyl acetate (3 x 100ml). The combined organic extract was washed with water (50ml), brine (50ml), dried over sodium sulphate and concentrated under vacuo to get the desired crude product. The crude product was purified by column chromatography using normal phase silica gel. The desired product eluted at around 1-5% methanol in dichloromethane. Evaporation of the product fractions gave 4g (yield, 58%) of desired compound as yellow solid. LC-MS: m/z=256.43 (M+H).

[00326] Step 3: Preparation of methyl 2-(3-(5-chloro-2-hydroxyphenyl) propylamino) acetate

[00327] To a solution of methyl 2-(3-(5-chloro-2-hydroxyphenyl) allylamino) acetate (3.5g, 13.6mmol) in methanol (80ml) was carefully added 10% Palladium on carbon with 50% moisture (0.145g, 1.3mmol). Hydrogen gas was then bubbled into the reaction mixture at room temperature for a period of 30 minutes. After completion of the reaction, the reaction mixture was filtered through celite. The celite bed was carefully washed with some amount of methanol. The filtrate thus obtained was concentrated under vacuo to afford 3g (yield, 85%) of compound as colorless liquid and used as is in the next step. LC-MS: m/z=258.5(M+H).

[00328] Step 4: Preparation of methyl 2-(3-(2-(4-(N-(tert-butoxycarbonyl)-N-(thiazol-4-yl) sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl) propylamino) acetate

[00329] To a solution methyl 2-(3-(5-chloro-2-hydroxyphenyl) propylamino) acetate (0.7g, 2.7mmol) in DMF (8ml) was added K_2CO_3 (1.2g, 8.1mmol) in one portion under nitrogen atmosphere at room temperature. The resulting reaction mixture was then stirred at room temperature for 15 minutes. To the above mixture was added tert-butyl 5-chloro-2,4-difluorophenylsulfonyl(thiazol-4-yl)carbamate (1.22g, 2.9mmol) at room temperature and the resulting reaction mixture was stirred at room temperature for 3hrs. After completion of reaction, water (10ml) was added and the resulting mixture was extracted with ethyl acetate (3 x 25ml). The combined organic extract was washed with water (20ml), brine (20ml), dried over sodium sulphate and concentrated under vacuo. The crude product was purified by column chromatography using normal phase silica gel. The desired product eluted at around 20 to 25% Ethyl acetate in Hexane. Evaporation of the product fractions gave 0.6g (yield, 36%)of desired compound as a solid. LC-MS: m/z = 648.4 (M+H).

[00330] Step 5: Preparation of 2-(3-(2-(4-(N-(tert-butoxycarbonyl)- N-(thiazol-4-yl)sulfamoyl) -2-chloro-5-fluorophenoxy)-5-chlorophenyl)propylamino)acetic acid

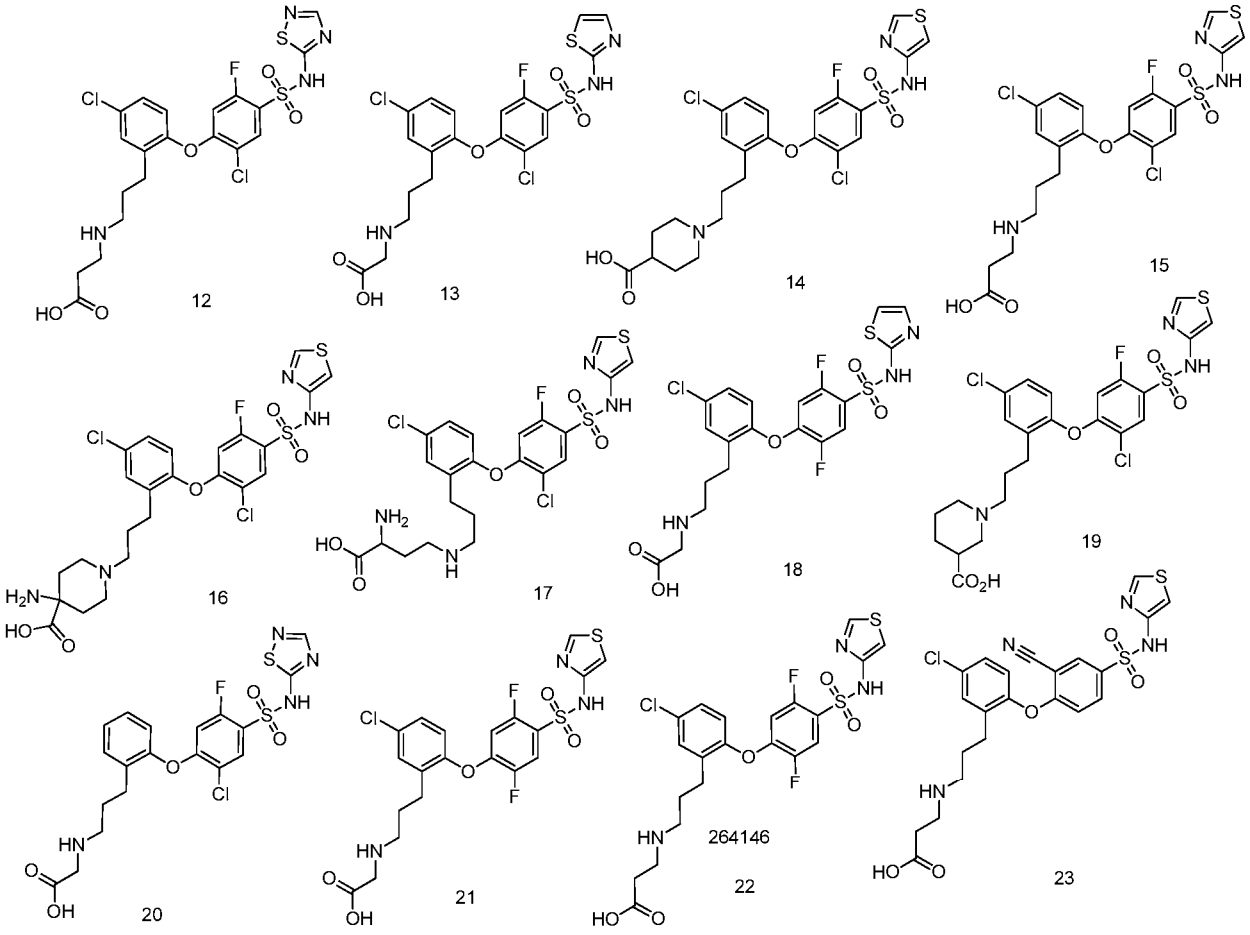
[00331] To the solution of methyl 2-(3-(2-(4-(N-(tert-butoxycarbonyl)-N-(thiazol-4-yl) sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl) propylamino) acetate (0.6g, 0.9mmol) in THF (10mL) was added a solution of lithium hydroxide monohydrate (0.0529, 4.6mmol) in water (6ml) at room temperature. The resulting reaction mixture was stirred at room temperature for 3 hours. After completion of reaction ice cold water (15ml) was added in to the reaction mixture, the resulting mixture was then acidified between 4-6 pH with aqueous 1N hydrochloric acid. The resulting acidic aqueous was extracted with ethyl acetate (3 x 25ml). The combined organic extract was washed with water (20ml), brine (20ml), dried over sodium sulphate and concentrated under vacuo to afford 0.5g (yield, 85%) of compound as white solid. This material was used in the next step as is.

[00332] Step 6: Preparation of 2-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-thiazol-4-ylsulfamoyl) phenoxy) phenyl) propylamino) acetic acid

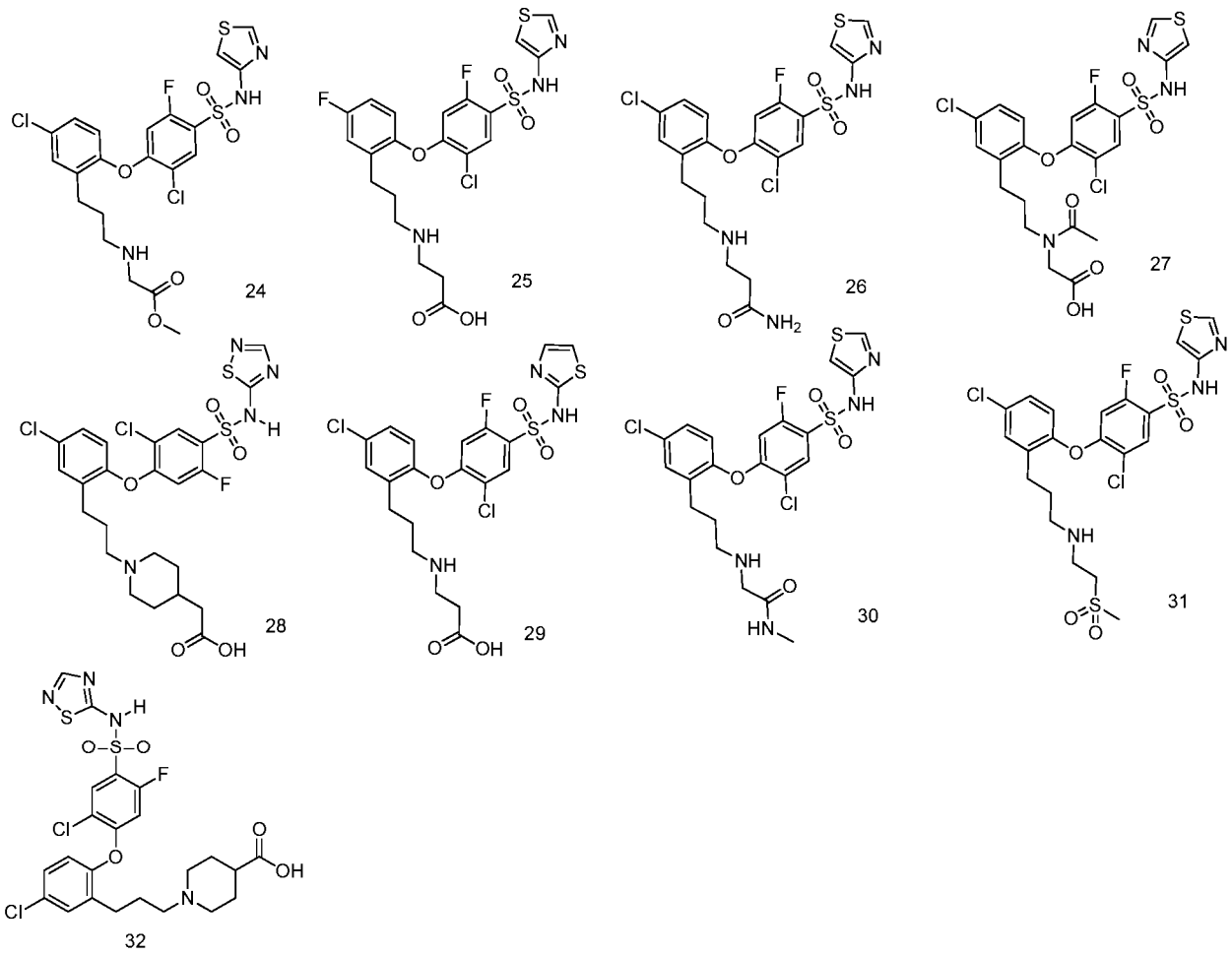
[00333] To the solution of 2-(3-(2-(4-(N-(tert-butoxycarbonyl)-N-(thiazol-4-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propylamino)acetic acid (0.5 g, 0.78mmol) in dichloromethane (15ml) was added drop-wise a 4N solution of hydrochloric acid in ethyl acetate (0.5ml) at room temperature. The resulting reaction mixture was stirred room temperature for 2 hours. After completion of reaction, pentane (20ml) was added in to the reaction mixture which resulted in precipitation of solid. The solvent layer was decanted off; the solid thus obtained was washed twice with pentane (15ml) and dried under vacuo. The resulting crude material was further purified by Prep HPLC using 0.1% hydrochloric acid in Water: Acetonitrile mobile phase. Evaporation of the pure product fractions obtained from Prep HPLC provided HCl salt of the desired product (0.16g, 38% yield). LC-MS: m/z = 533.9 (M+H). 1H-NMR (MeOD), δ 8.77 (d, *J* = 2.4 Hz, 1H), 8.03 (d, *J* = 6.8 Hz, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.37 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.76 (d, *J* = 10.8 Hz, 1H), 3.8 (s, 2H), 3.09-3.05 (m, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.04-2.01 (m, 2H).

[00334] The compounds 12 to 32 were synthesized according to the synthetic scheme described for example 11.

Scheme 8



Scheme 9



Example 12: 3-((3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)amino)propanoic acid

[00335] Compound **12** was synthesized according to the procedure described for the synthesis of compound **11** by replacing glycine methyl ester with beta alanine methyl ester in step 2, and replacing tert-butyl 5-chloro-2,4-difluorophenylsulfonyl(thiazol-4-yl)carbamate with 5-chloro-N-(2,4-dimethoxybenzyl)-2,4-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide in step 4. LC-MS: m/z = 549.6 (M+H). 1H-NMR (MeOD), δ 8.27 (s, 1H), 8.05 (d, *J* = 7.2 Hz, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.36 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.78 (d, *J* = 6.4 Hz, 1H), 3.26 (t, *J* = 6.4 Hz, 2H), 3.08 (t, *J* = 7.6 Hz, 2H), 2.68 – 2.75 (m, 4H), 2.01 – 2.06 (m, 2H).

Example 13: 2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid

[00336] Compound **13** was synthesized according to the procedure described for the synthesis of compound **11** by replacing tert-butyl 5-chloro-2,4-difluorophenylsulfonyl(thiazol-4-yl)carbamate with 5-chloro-N-(2,4-dimethoxybenzyl)-2,4-difluoro-N-(thiazol-2-yl)benzenesulfonamide in step 4. LC-MS: m/z = 533.8 (M+H). 1H-NMR (MeOD), δ 7.94 (d, *J* = 6.8 Hz, 1H), 7.52 (d, *J* = 5.8, 1H), 7.35 – 7.38 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.33 (d, *J* = 4.4 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 6.91 – 6.94 (m, 2H), 3.60 (s, 2H), 2.80 (m, 2H), 2.56 (m, 2H), 1.99 (m, 2H).

Example 14: 1-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)piperidine-4-carboxylic acid

[00337] Compound **14** was synthesized according to the procedure described for the synthesis of compound **11** by replacing glycine methyl ester with methyl piperidine-4-carboxylate in step 2. LC-MS: m/z = 589.8 (M+H).

Example 15: 3-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid

[00338] Compound **15** was synthesized according to the procedure described for the synthesis of compound **11** by replacing glycine methyl ester with beta alanine methyl ester in step 2. LC-MS: m/z = 547.8 (M+H). 1H-NMR (MeOD), δ 8.77 (d, *J* = 2.0 Hz, 1H), 8.03 (d, *J* = 10.8 Hz, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.35 – 7.38 (m, 1H), 7.12 (d, *J* = 2.8 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* =10.4 Hz, 1H), 3.26 (br, 2H), 3.07 (br, 2H), 2.67 – 2.76 (m, 4H), 2.02 (br, 2H).

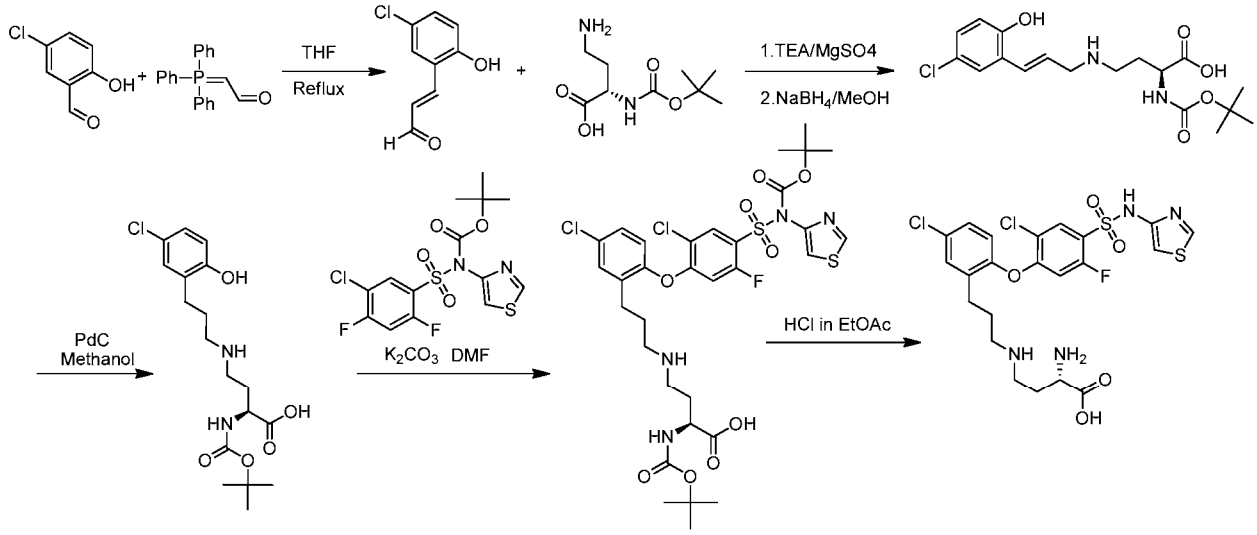
Example 16: 4-amino-1-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)piperidine-4-carboxylic acid

[00339] Compound **16** was synthesized according to the procedure described for the synthesis of compound **11** by replacing glycine methyl ester with methyl 4-((tert-butoxycarbonyl)amino)piperidine-4-carboxylate in step 2. LC-MS: m/z = 602.8 (M+H). 1H-

NMR (MeOD), δ 8.77 (d, *J* = 2.0 Hz, 1H), 8.02 (d, *J* = 7.2 Hz, 1H), 7.52 (d, *J* = 2.8 Hz, 1H), 7.36 – 7.38 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.12 (d, *J* = 2.0 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.77 (d, *J* = 10.4 Hz, 1H), 3.25 – 3.70 (m, 6H) 2.67 – 2.71 (m, 2H), 2.50 (br, 2H), 2.27 (br, 2H), 2.12 (br, 2H).

Example 17: 2-amino-4-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)butanoic acid

Scheme 10



[00340] Step 1: Preparation of (S)-4-amino-2-(tert-butoxycarbonylamino)butanoic acid

[00341] To a solution of (S)-5-amino-2-(tert-butoxycarbonylamino)-5-oxopentanoic acid (2g, 8.1mmol) in DMF: water (1:1,v/v,18ml) was added pyridine (1.3ml, 16.2mmol). The resulting reaction mixture was stirred at room temperature for 5-10 minutes. Iodobenzene diacetate (3.92g, 12.1mmol) was added and further stirred for 4 hours. After completion of reaction D.M. water (100ml) was added and the resulting mixture was extracted with ethyl acetate (3 x 100ml). The combined organic extracts was washed with D.M. water (100ml), brine (100ml), dried over sodium sulphate and concentrated under vacuo to get the desired crude product. The crude product was purified by triturating with diethyl ether. Evaporation of the product fractions gave 1.1g (yield, 62%) of desired compound as brown solid. LC-MS: m/z = 219.1(M+H).

[00342] Step 2: Preparation of (E)-3-(5-chloro-2-hydroxyphenyl)acrylaldehyde

[00343] To a solution of 5-chloro-2-hydroxybenzaldehyde (20g, 127mmol) in THF (300ml) was added (Formylmethylene)triphenylphosphorane (43g, 140mmol) at room temperature. The resulting reaction mixture was then refluxed at 100^0C for 20 hrs. After completion of reaction, the reaction mixture was allowed to cool to room temperature. D.M. water (200ml) was added and the resulting mixture was extracted with ethyl acetate (3 x 250ml). The combined organic extract was washed with D.M. water (200ml), brine (200ml), dried over sodium sulphate and concentrated under vacuo to get the desired crude product. The crude product was purified by column chromatography using normal phase silica gel. The desired product eluted at around 20- 30% ethyl acetate in hexane. Evaporation of the product fractions gave 20g (yield, 87%) of the desired compound as yellow solid. LC-MS: m/z = 183.4(M+H).

[00344] Step 3: (S,E)-2-(tert-butoxycarbonylamino)-4-(3-(5-chloro-2-hydroxyphenyl)allylamino)butanoic acid

[00345] To a solution of 3-(5-chloro-2-hydroxyphenyl)acrylaldehyde (0.5g, 3.2mmol)and (S)-4-amino-2-(tert-butoxycarbonylamino)butanoic acid (0.769g, 3.52mmol) in dichloromethane (80ml) was added magnesium sulphate (0.77g, 6.4mmol) and triethylamine (1.34ml, 9.615mmol) at room temperature. The above reaction mixture was stirred at room temperature for 12 hours. The resulting reaction mixture was then concentrated under vacuo. The concentrated mass thus obtained was dissolved in methanol (20ml) and cooled to a temperature between 5-10^0C. To the above mixture, sodium borohydride (0.36g, 9.61mmol) was added in small portions over a period of 10 minutes, during addition temperature of the reaction mixture was maintained between 10-20^0C. After completion of addition, the resulting reaction mixture was allowed to stir at room temperature for 2 hours. After completion of reaction, the reaction mixture was concentrated under vacuo. D.M. water (40ml) was added to the above crude mass and the resulting mixture was extracted with ethyl acetate (3 x 60ml). The combined organic extract was washed with D.M. water (50ml), brine (50ml), dried over sodium sulphate and concentrated under vacuo to get the desired crude product. The crude product was purified by column chromatography using normal phase silica gel. The desired product eluted at around 1-5%

methanol in dichloromethane. Evaporation of the product fractions gave 0.4g (yield, 32.5%) of the desired compound as a brown liquid. LC-MS: m/z = 385.2(M+H).

[00346] Step 4: (S)-2-(tert-butoxycarbonylamino)-4-(3-(5-chloro-2-hydroxyphenyl)propylamino)butanoic acid

[00347] To a solution of (S,E)-2-(tert-butoxycarbonylamino)-4-(3-(5-chloro-2-hydroxyphenyl)allylamino)butanoic acid (0.4g, 13.6mmol) in methanol (10ml) was carefully added 10% Palladium on carbon with 50% moisture (0.120g, 1.3mmol). Hydrogen gas was then bubbled into the reaction mixture at room temperature for a period of 15-20 minutes. After completion of the reaction, the reaction mixture was filtered through celite hyflow. The celite bed was carefully washed with some amount of methanol. The filtrate thus obtained was concentrated under vacuo to afford 0.35g (yield, 87.06%) of the desired compound as a colorless liquid. LC-MS: m/z = 387.4(M+H).

[00348] Note: For this particular step, we also observed occurrence of dechlorination, its proportion remained variable. This step was thus monitored cautiously and worked up soon upon completion.

[00349] Step 5: (S)-4-(3-(2-(4-(N-(tert-butoxycarbonyl)-N-(thiazol-4-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propylamino)-2-(tert-butoxycarbonylamino)butanoic acid

[00350] To a solution (S)-2-(tert-butoxycarbonylamino)-4-(3-(5-chloro-2-hydroxyphenyl)propylamino)butanoic acid (0.350g, 2.7mmol) in DMF (0.7ml) was added K_2CO_3 (0.375g, 2.7mmol) in one portion under nitrogen atmosphere at room temperature. The resulting reaction mixture was then stirred at room temperature for 15 minutes. To the above mixture was added tert-butyl 5-chloro-2,4-difluorophenylsulfonyl(thiazol-4-yl) carbamate (0.408g, 0.99mmol) and the resulting reaction mixture was stirred at room temperature for 3 hours. After completion of reaction, D.M. water (20ml) was added and the resulting mixture was extracted with ethyl acetate (3 x 30ml). The combined organic extract was washed with Ice cold water (100ml), brine (50ml), dried over sodium sulphate and concentrated under vacuo. The crude product was purified by column chromatography using normal phase silica gel. The

desired product eluted at around 1 to 2% Methanol in DCM. Evaporation of the product fractions gave 0.4g (yield, 56.8%) of the desired compound as a brown liquid. LC-MS: m/z = 777.6(M+H).

[00351] Step 6: Preparation of (S)-2-amino-4-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-thiazol-4-ylsulfamoyl)phenoxy) phenyl)propylamino)butanoic acid

[00352] To a solution of (S)-4-(3-(2-(4-(N-(tert-butoxycarbonyl)-N-(thiazol-4-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propylamino)-2-(tert-butoxycarbonylamino)butanoic acid (0.4g, 0.78mmol) in dichloromethane (10ml) was added drop-wise a 4N solution of hydrochloric acid in ethyl acetate (2ml) at room temperature. The resulting reaction mixture was stirred room temperature for 2 hours. After completion of reaction, pentane (20ml) was added in to the reaction mixture which resulted in precipitation of solid. The solvent layer was decanted off; the solid thus obtained was washed twice with pentane (15ml) and dried under vacuo. The resulting crude material was further purified by Prep HPLC using 0.1% Formic acid in Water: Acetonitrile mobile phase. Evaporation of the pure product fractions obtained from Prep HPLC provided the desired product as HCl salt (0.0253g, 8.6% yield). LC-MS: m/z = 576.8 (M+H).

Example 18: 2-((3-(5-chloro-2-(2,5-difluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid

[00353] Compound **18** was synthesized according to the procedure described for the synthesis of compound **11** by replacing tert-butyl 5-chloro-2,4-difluorophenylsulfonyl(thiazol-4-yl)carbamate with N-(2,4-dimethoxybenzyl)-2,4,5-trifluoro-N-(thiazol-2-yl)benzenesulfonamide in step 4. LC-MS: m/z = 517.8 (M+H). 1H-NMR (MeOD), δ 7.81 – 7.85 (dd, *J* = 6.4, 10.4 Hz, 1H), 7.46 (d, *J* = 6.4, 1H), 7.31 – 7.34 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.17 (d, *J* = 4.8 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.86 – 6.90 (dd, *J* = 6.4, 10.0 Hz, 1H), 6.81 (d, *J* = 4.8 Hz, 1H), 3.92 (s, 2H), 3.08 – 3.12 (m, 2H), 2.75 (t, J = 8.0 Hz, 2H), 2.03 – 2.08 (m, 2H).

Example 19: 1-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)piperidine-3-carboxylic acid

[00354] Compound **19** was synthesized according to the procedure described for the synthesis of compound **11** by replacing glycine methyl ester with methyl piperidine-3-carboxylate in step 2. LC-MS: m/z = 589.8 (M+H).

Example 20: 2-((3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)phenyl)propyl)amino)acetic acid

[00355] Compound **20** was synthesized according to the procedure described for the synthesis of compound **11** by replacing 5-chloro-2-hydroxybenzaldehyde with 2-hydroxybenzaldehyde in step 1. LC-MS: m/z = 500.8 (M+H). 1H-NMR (MeOD), δ 8.90 (s, 2H), 8.51 (s, 1H), 7.97 (d, *J* = 7.2 Hz, 1H), 7.41 – 7.44 (dd, *J* = 1.6, 7.2 Hz, 1H), 7.26 – 7.34 (m, 2H), 7.07 (dd, *J* = 1.2, 8.0 Hz, 1H), 6.81 (d, *J* =10.8 Hz, 1H), 3.89 (s, 2H), 2.93 (br, 2H), 2.57 – 2.61 (m, 2H), 1.92 (br, 2H).

Example 21: 2-((3-(5-chloro-2-(2,5-difluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid

[00356] Compound **21** was synthesized according to the procedure described for the synthesis of compound **11** by replacing tert-butyl 5-chloro-2,4-difluorophenylsulfonyl(thiazol-4-yl)carbamate with tert-butyl 2,4,5-trfluorophenylsulfonyl(thiazol-4-yl)carbamate in step 4. LC-MS: m/z = 517.8 (M+H). 1H-NMR (MeOD), δ 8.77 (d, *J* = 2.0 Hz, 1H), 7.79 – 7.83 (dd, *J* = 6.4, 10.0 Hz, 1H), 7.47 (d, *J* = 2.4 Hz, 1H), 7.32 – 7.35 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.11 (d, *J* = 2.4 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.85 – 6.89 (dd, *J* = 6.4,10.4 Hz, 1H), 3.92 (s, 2H), 3.09 – 3.16 (m, 2H), 2.73 (t, *J* = 7.6 Hz, 2H), 1.99 – 2.07 (m, 2H).

Example 22: 3-((3-(5-chloro-2-(2,5-difluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid

[00357] Compound **22** was synthesized according to the procedure described for the synthesis of compound **11** by replacing glycine methyl ester with beta alanine methyl ester in step 2, and replacing tert-butyl 5-chloro-2,4-difluorophenylsulfonyl(thiazol-4-yl)carbamate with

tert-butyl 2,4,5-trfluorophenylsulfonyl(thiazol-4-yl)carbamate in step 4. LC-MS: m/z = 531.8 (M+H). 1H-NMR (MeOD), δ 8.78 (d, *J* = 2.4 Hz, 1H), 7.79 – 7.83 (dd, *J* = 6.4, 10.4 Hz, 1H), 7.47 (d, *J* = 2.4 Hz, 1H), 7.32 – 7.35 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.11 (d, *J* = 2.4 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.85 – 6.90 (dd, *J* = 6.4,10.4 Hz, 1H), 3.27 (t, *J* = 6.8 Hz, 2H), 3.07 (t, *J* = 8.0 Hz, 2H), 2.71 – 2.78 (m, 4H), 1.97 – 2.05 (m, 2H).

Example 23: 3-((3-(5-chloro-2-(2-cyano-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid

[00358] Compound **23** was synthesized according to the procedure described for the synthesis of compound **11** by replacing glycine methyl ester with beta alanine methyl ester in step 2, and replacing tert-butyl 5-chloro-2,4-difluorophenylsulfonyl(thiazol-4-yl)carbamate with tert-butyl (3-cyano-4-fluorophenyl)sulfonyl(thiazol-4-yl)carbamate in step 4. LC-MS: m/z = 520.9 (M+H). 1H-NMR (MeOD), δ 8.77 (d, *J* = 2.0 Hz,1H), 8.30 (d, *J* = 2.0 Hz, 1H), 8.03 (dd, *J* = 2.4, 9.2 Hz, 1H), 7.52 (d, *J* = 2.4 Hz, 1H), 7.39 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 7.14 (s, 1H), 6.96 (d, *J* = 9.2 Hz, 1H), 3.09 (t, J = 6.8 Hz, 2H), 3.09 (t, J = 8.0 Hz, 2H), 2.76 (t, J = 6.4 Hz, 2H), 2.69 (t, J = 8.0 Hz, 2H), 1.99 – 2.07 (m, 2H).

Example 24: methyl 2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetate

[00359] Compound **24** was synthesized according to the procedure described for the synthesis of compound **11** without hydrolysis of methyl ester (step 5). LC-MS: m/z = 548.4 (M+H). 1H-NMR (MeOD), δ 8.77 (d, *J* = 2.4 Hz, 1H), 8.02 (d, *J* = 6.8 Hz, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.35 – 7.38 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.75 (d, *J* = 10.4 Hz, 1H), 3.99 (s, 2H), 3.85 (s, 3H), 3.08-3.12 (m, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.00 - 2.08 (m, 2H).

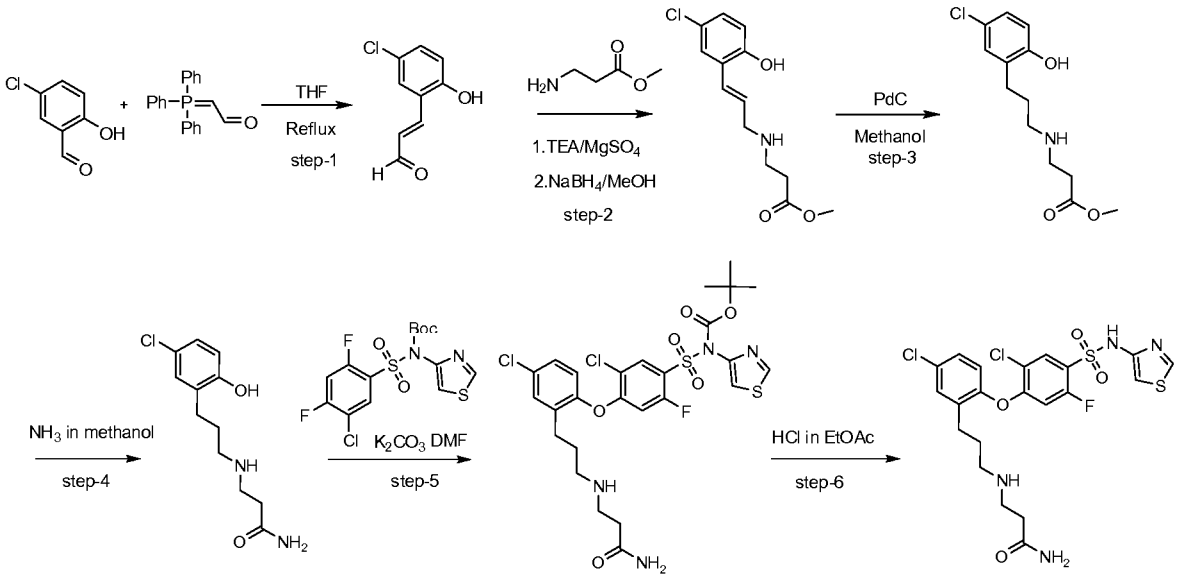
Example 25: 3-((3-(2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)-5-fluorophenyl)propyl)amino)propanoic acid

[00360] Compound **25** was synthesized according to the procedure described for the synthesis of compound **11** by replacing 5-chloro-2-hydroxybenzaldehyde with 5-fluoro-2-

hydroxybenzaldehyde in step 1, and replacing glycine methyl ester with beta alanine methyl ester in step 2. LC-MS: m/z = 531.9 (M+H). 1H-NMR (MeOD), δ 8.77 (d, *J* = 2.4 Hz,1H), 8.01 (d, *J* = 6.8 Hz, 1H), 7.23 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.11 – 7.13 (m, 3H), 6.65 (d, *J* = 10.8 Hz, 1H), 3.25 (t, J = 6.8 Hz, 2H), 3.06 (t, J = 8.0 Hz, 2H), 2.73 (t, J = 6.4 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H), 1.99 – 2.03 (m, 2H).

Example 26: 3-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanamide

Scheme 11



[00361] Step 1: Preparation of 3-(5-chloro-2-hydroxyphenyl)acrylaldehyde

[00362] To a solution of 5-chloro-2-hydroxybenzaldehyde (20g, 127mmol) in THF (300ml) was added (formylmethylene)triphenylphosphorane (43g, 140mmol) at room temperature. The resulting reaction mixture was then refluxed at 100^{0}C for 20 hrs. After completion of reaction, the reaction mixture was allowed to cool to room temperature. Water (200ml) was added and the resulting mixture was extracted with ethyl acetate (3 x 250ml). The combined organic extract was washed with water (200ml), brine (200ml), dried over sodium sulphate and concentrated under vacuo to get the desired crude product. The crude product was purified by column chromatography using normal phase silica gel. The desired product eluted at around 20- 30% ethyl acetate in hexane. Evaporation of the product fractions gave 20g (yield, 87%) of desired compound as yellow solid. LC-MS: m/z= 181.34(M-H).

[00363] Step 2: Preparation of methyl 3-[3-(5-chloro-2-hydroxyphenyl)allylamino]propanoate)

[00364] To a solution of 3-(5-chloro-2-hydroxyphenyl)acrylaldehyde (1.0g, 5.47mmol) and β-Alanine methyl ester hydrochloride (0.917g, 6.57mmol) in DCM (20ml) was added magnesium sulphate (1.317g, 1.09mmol) and TEA (2.3ml, 16.41mmol) at room temperature and the resulting reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was then concentrated under vacuo. The concentrated mass thus obtained was dissolved in methanol (20ml) and cooled to 5-10 ^{0}C. To this cold reaction mixture, sodium borohydrate (0.620g, 16.41mmol) was then added in small portions over a period of 10-20mins, during addition the temperature was maintained in between 10-20^{0}C. After completion of addition the resulting reaction mixture was allowed to stir at room temperature for 2 hours. After completion of the reaction, it was concentrated under vacuo. To the resulting crude mass water (50ml) was added and the mixture was extracted with EtOAc (3 x 25ml). The combined organic extract was washed with water (20ml), brine (20ml), dried over sodium sulphate and concentrated under vacuo to get the desired crude product. The crude product was purified by column chromatography using normal phase silica gel. The desired product eluted at around 1-5% Methanol in DCM. Evaporation of the product fractions gave 0.9g (yield, 61%) of desired compound as white solid. LC-MS: m/z = 270.6 (M+H).

[00365] Step 3: Preparation of methyl 3-[3-(5-chloro-2-hydroxyphenyl)propylamino] propanoate)

[00366] To a solution of 3-[3-(5-chloro-2-hydroxyphenyl)allylamino]propanoate) (0.35g, 1.3mmol) in methanol (20ml) was carefully added 10% Palladium on carbon with 50% moisture (0.104g, 0.065mmol). Hydrogen gas was then bubbled into the reaction mixture at room temperature for a period of 30 mins. The reaction mixture was monitored on TLC using ethyl acetate as mobile phase. After completion of the reaction, the reaction mixture was filtered through celite. The celite bed was carefully washed with some amount of methanol. The filtrate thus obtained was concentrated under vacuo to afford 0.3g (yield, 85%) of desired compound colorless liquid. m/z = 272.6 (M+H).

[00367] Step 4: Preparation of 3-[3-(5-chloro-2-hydroxyphenyl)propylamino] propanamide)

[00368] A solution of methyl 3-[3-(5-chloro-2-hydroxyphenyl)propylamino] propanoate) (0.3g, 1.08mmol) in methanolic ammonia (10mL) was heated at 100^0C in sealed tube (35mL) for a time period of 12 hours. After completion of reaction methanol was evaporated under vacuo. The crude product was purified by column chromatography using normal phase silica gel. The desired product eluted at around 30- 40% ethyl acetate in hexane. Evaporation of the product fractions gave 0.16g (yield, 33.9%) of the desired compound as a colorless liquid. m/z = 257.2 (M+H).

[00369] Step 5: Preparation of methyl 3-(3-(2-(4-(*N*-(*tert*-butoxycarbonyl)-*N*-(thiazol-4-yl) sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl) propylamino) propanoate

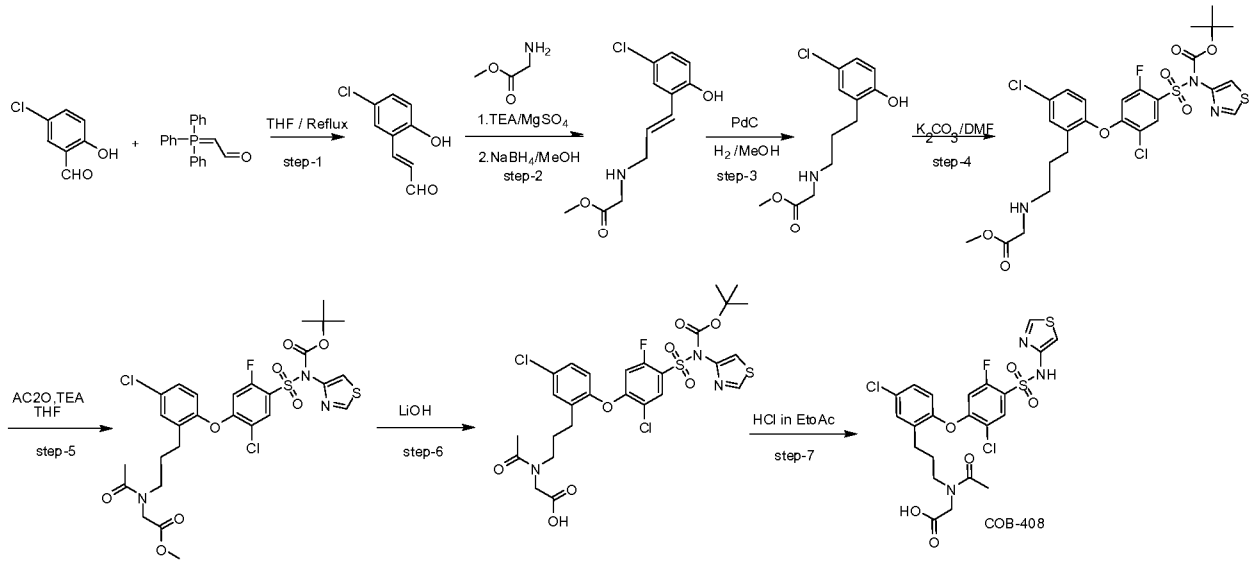
[00370] To a solution 3-[3-(5-chloro-2-hydroxyphenyl)propylamino] propanoate) (0.09g, 0.35mmol) in DMF (2ml) was added K_2CO_3 (0.145, 1.05mmol) in one portion under nitrogen atmosphere at room temperature. The resulting reaction mixture was stirred at room temperature for 15 minutes. To the above mixture was added *tert*-butyl 5-chloro-2,4-difluorophenylsulfonyl(thiazol-4-yl)carbamate (0.143g, 0.35mmol) and the resulting mixture was stirred at room temperature for 3 hours. After completion of reaction, water (10ml) was added and the resulting mixture was extracted with ethyl acetate (3 x 25ml). The combined organic extract was washed with water (20ml), brine (20ml), dried over sodium sulphate and concentrated under vacuo. The crude product was purified by column chromatography using normal phase silica gel. The desired product eluted at around 20 to 25% ethyl acetate in hexane. Evaporation of the product fractions gave 0.15g (yield, 66.2%) of desired compound as a solid. This material was used for the next step without any further purification and analysis. The material was used directly for the next step.

[00371] Step 6: Preparation of 3-(3-(5-chloro-2(2-chloro-5-fluoro-4-(*N* –thiazol-4-ylsulfamoyl)phenoxy)phenyl)propylamino)propanamide fluorophenylsulfonyl(thiazol-4-yl)carbamate

[00372] To a solution of 3-(3-(2-(4-(*N*-(*tert*-butoxycarbonyl)-*N*-(thiazol-4-yl) sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl) propylamino) propanoate (0.15g, 0.23mmol) in dichloromethane (5ml) was added drop-wise a 4N solution of hydrochloric acid in ethyl acetate (0.5ml) at room temperature. The resulting reaction mixture was stirred room temperature for 2 hours. After completion of reaction, pentane (20ml) was added in to the reaction mixture which resulted in precipitation of solid. The solvent layer was decanted off; the solid thus obtained was washed twice with pentane (15ml) and dried under vacuo. The resulting crude material was further purified by Prep HPLC using 0.1% Formic acid in Water:Acetonitrile mobile phase. Evaporation of the pure product fractions obtained from Prep HPLC provided the desired product as HCl salt. (0.009g, 7.1% yield). LC-MS: m/z = 548.8 (M+H). 1H-NMR (MeOD), δ 8.75 (d, *J* = 2.4 Hz, 1H), 8.01 (d, *J* = 7.2 Hz, 1H), 7.48 (d, *J* = 2.4 Hz, 1H), 7.34 – 7.37 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 10.4 Hz, 1H), 3.22 (t, *J* = 6.4 Hz, 2H), 3.02 – 3.06 (m, 2H), 2.62 – 2.70 (m, 4H), 1.99 – 2.03 (m, 2H).

Example 27: 2-(N-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)acetamido)acetic acid

Scheme 12



[00373] Step 1: Preparation of (E)-3-(5-chloro-2-hydroxyphenyl) acrylaldehyde

[00374] To a solution of 5-chloro-2-hydroxybenzaldehyde (20g, 127 mmol) in THF (300 ml) was added (formylmethylene)triphenylphosphorane (43g, 140mmol) at room temperature. The resulting reaction mixture was then refluxed at 100^0C for 20 hrs. After completion of reaction, the reaction mixture was allowed to cool to room temperature. Water (200 ml) was added and the resulting mixture was extracted with ethyl acetate (3 x 250ml). The combined organic extract was washed with water (200ml), brine (200 ml), dried over sodium sulphate and concentrated under vacuo to get the desired crude product. The crude product was purified by column chromatography using normal phase silica gel. The desired product eluted at around 20-30% ethyl acetate in hexane. Evaporation of the product fractions gave 20g (yield, 87%) of the desired compound as a yellow solid LC-MS: m/z = 183.4(M+H).

[00375] Step 2: Preparation of (E)-methyl 2-(3-(5-chloro-2-hydroxyphenyl)allylamino)acetate

[00376] To a solution of (E)-3-(5-chloro-2-hydroxyphenyl)acrylaldehyde (1.0g, 5.4mmol) and glycine methyl ester hydrochloride(0.590g, 6.55mmol) in dichloromethane (20ml) was added magnesium sulphate (1.5g, 10.9mmol) and triethylamine (2.28ml, 16.38mmol) at room temperature. The above reaction mixture was stirred at room temperature for 12 hours. The resulting reaction mixture was then concentrated under vacuo. The concentrated mass thus obtained was dissolved in methanol (20ml) and cooled to a temperature between 5-10^0C. To the above mixture, sodium borohydride (0.606g, 16.38mmol) was added in small portions over a period of 10 minutes; during addition temperature of the reaction mixture was maintained between 10-20^0C. After completion of addition, the resulting reaction mixture was allowed to stir at room temperature for 2 hours. After completion of reaction, the reaction mixture was concentrated under vacuo. Water (40ml) was added to the above crude mass and the resulting mixture was extracted with ethyl acetate (3 x 60ml). The combined organic extract was washed with water (50ml), brine (50ml), dried over sodium sulphate and concentrated under vacuo to get the desired crude product. The crude product was purified by column chromatography using normal phase silica gel. The desired product eluted at around 2-3% methanol in

dichloromethane. Evaporation of the product fractions gave 0.8g (yield, 57.4%) of the desired compound as a brown liquid. LC-MS: m/z = 256.07(M+H).

[00377] Step 3: Preparation of methyl 2-(3-(5-chloro-2-hydroxyphenyl)propylamino)acetate

[00378] To a solution of (E)-methyl 2-(3-(5-chloro-2-hydroxyphenyl)allylamino)acetate (0.8g, 3.13mmol) in methanol (50ml) was carefully added Palladium hydroxide (0.199g, 0.09mmol). Hydrogen gas was then bubbled into the reaction mixture at room temperature for a period of 30 minutes. After completion of the reaction, the reaction mixture was filtered through celite. The celite bed was carefully washed with some amount of methanol. The filtrate thus obtained was concentrated under vacuo to afford 0.7g (yield, 86.81%) of compound as colorless liquid. LC-MS: m/z = 258.07(M+H).

[00379] Step 4: Preparation of methyl 2-(3-(2-(4-(N-(tert-butoxycarbonyl)-N-(thiazol-4-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propylamino)acetate

[00380] To a solution of methyl 2-(3-(5-chloro-2-hydroxyphenyl)propylamino)acetate (0.7g, 2.72mmol) in DMF (7ml) was added K_2CO_3 (1.12g, 8.17mmol) in one portion under nitrogen atmosphere at room temperature. The resulting reaction mixture was then stirred at room temperature for 15 minutes. To the above mixture was added tert-butyl 5-chloro-2,4-difluorophenylsulfonyl(thiazol-4-yl)carbamate(1.22g, 2.996mmol) and the resulting reaction mixture was stirred at room temperature for 3 hours. After completion of reaction, water (20ml) was added and the resulting mixture was extracted with ethyl acetate (3 x 50ml). The combined organic extract was washed with water (20ml), brine (20ml), dried over sodium sulphate and concentrated under vacuo to afford 0.54 g (yield, 30.64%) of the compound as a white solid. LC-MS: m/z = 646.20(M-H).

[00381] Step 5: Preparation of methyl 2-(N-(3-(2-(4-(N-(tert-butoxycarbonyl)-N-(thiazol-4-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)acetamido)acetate.

[00382] To a solution of methyl 2-(3-(2-(4-(N-(tert-butoxycarbonyl)-N-(thiazol-4-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propylamino)acetate (0.35g, 0.54 mmol) in THF(5 mL) was added triethyl amine (0.22ml, 1.62mmol). The resulting reaction

mixture was stirred at 0^0C for 5-10 minutes. Acetic anhydride (0.102ml, 1.08mmol) was added at 0^0C. The resulting reaction mixture was then refluxed at 80^0C for 12 hours. To the reaction mixture water (30ml) was added and the resulting mixture was extracted with ethyl acetate (3 x 50ml). The combined organic extracts was washed with water (30ml), brine (30ml), dried over sodium sulphate and concentrated under vacuum to get the desired crude product. The crude product was purified by triturating with diethyl ether. Evaporation of the product fractions gave 0.35g (yield, 94.01%) of the desired compound as a brown solid. LC-MS: m/z = 690.5(M+H).

[00383] Step 6: Preparation of 2-(N-(3-(2-(4-(N-(tert-butoxycarbonyl)-N-(thiazol-4-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)acetamido)acetic acid

[00384] To the solution of methyl 2-(N-(3-(2-(4-(N-(tert-butoxycarbonyl)-N-(thiazol-4-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)acetamido)acetate (0.35g, 0.50mmol) in THF (5ml) was added a solution of lithium hydroxide monohydrate (0.212g, 5.07mmol) in water (0.5 ml) at room temperature. The resulting reaction mixture was stirred at room temperature for 3 hours. After completion of reaction ice cold water (15ml) was added in to the reaction mixture, the resulting mixture was then acidified between 4-6 pH with aqueous 1N hydrochloric acid. The resulting acidic aqueous was extracted with ethyl acetate (3 x 25ml). The combined organic extract was washed with water (20ml), brine (20ml), dried over sodium sulphate and concentrated under vacuo to afford 0.3g (yield, 87.49%) of the compound as a white solid. This material was directly used for next step without any further purification and analysis. LC-MS: m/z = 676.41(M+H).

[00385] Step 7: Preparation of 2-(N-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-thiazol-4-ylsulfamoyl) phenoxy) phenyl) propyl)acetamido)acetic acid

[00386] To the solution of 2-(N-(3-(2-(4-(N-(tert-butoxycarbonyl)-N-(thiazol-4-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)acetamido)acetic acid (0.3g, 0.44mmol) in dichloromethane (4ml) was added drop-wise a 4N solution of hydrochloric acid in ethyl acetate (1ml) at room temperature. The resulting reaction mixture was stirred room temperature for 2 hours. After completion of reaction, pentane (20ml) was added in to the reaction mixture which resulted in precipitation of solid. The solvent layer was decanted off; the solid thus obtained was washed twice with pentane (15ml) and dried under vacuo. The resulting

crude material was further purified by Prep HPLC using 0.1% Hydrochloric acid in water: acetonitrile mobile phase. Evaporation of the pure product fractions obtained from Prep HPLC provided the desired product as HCl salt (0.060g, 23.47% yield). LC-MS: m/z = 575.92(M+H).

Example 28: 2-(1-(3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)piperidin-4-yl)acetic acid

[00387] Compound **28** was synthesized according to the procedure described for the synthesis of compound **11** by replacing glycine methyl ester with methyl 2-(piperidin-4-yl)acetate in step 2, and replacing tert-butyl 5-chloro-2,4-difluorophenylsulfonyl(thiazol-4-yl)carbamate with 5-chloro-N-(2,4-dimethoxybenzyl)-2,4-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide in step 4. LC-MS: m/z = 601.2 (M+H).

Example 29: 3-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid

[00388] Compound **29** was synthesized according to the procedure described for the synthesis of compound **11** by replacing glycine methyl ester with beta alanine methyl ester in step 2, and replacing tert-butyl 5-chloro-2,4-difluorophenylsulfonyl(thiazol-4-yl)carbamate with 5-chloro-N-(2,4-dimethoxybenzyl)-2,4-difluoro-N-(thiazol-2-yl)benzenesulfonamide in step 4. LC-MS: m/z = 547.9 (M+H). 1H-NMR (MeOD), δ 8.05 (d, *J* = 6.8 Hz,1H), 7.49 (d, *J* = 2.8 Hz, 1H), 7.34 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.17 (d, *J* = 4.4 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 4.4 Hz, 1H), 6.75 (d, *J* = 10.4 Hz, 1H), 3.14 (t, J = 6.4 Hz, 2H), 3.04 (t, J = 8.0 Hz, 2H), 2.71 (t, J = 8.0 Hz, 2H), 2.49 (t, J = 6.4 Hz, 2H), 2.00 – 2.03 (m, 2H).

Example 30: 2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)-N-methylacetamide

[00389] Compound **30** was synthesized according to the procedure described for the synthesis of compound **11** by replacing glycine methyl ester with 2-amino-N-methylacetamide in step 2. LC-MS: m/z = 547.1 (M+H). 1H-NMR (MeOD), δ 8.77 (d, *J* = 2.4 Hz,1H), 8.01 (d, *J* = 7.2 Hz, 1H), 7.48 (d, *J* = 2.4 Hz, 1H), 7.35 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.10 (d, *J* = 2.0 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.73 (d, *J* = 10.4 Hz, 1H), 3.70 (s, 2H), 2.97 – 3.02 (m, 2H), 2.80 (s, 3H), 2.65 – 2.69 (m, 2H), 1.96 – 2.06 (m, 2H).

Example 31: 5-chloro-4-(4-chloro-2-(3-((2-(methylsulfonyl)ethyl)amino)propyl)phenoxy)-2-fluoro-N-(thiazol-4-yl)benzenesulfonamide

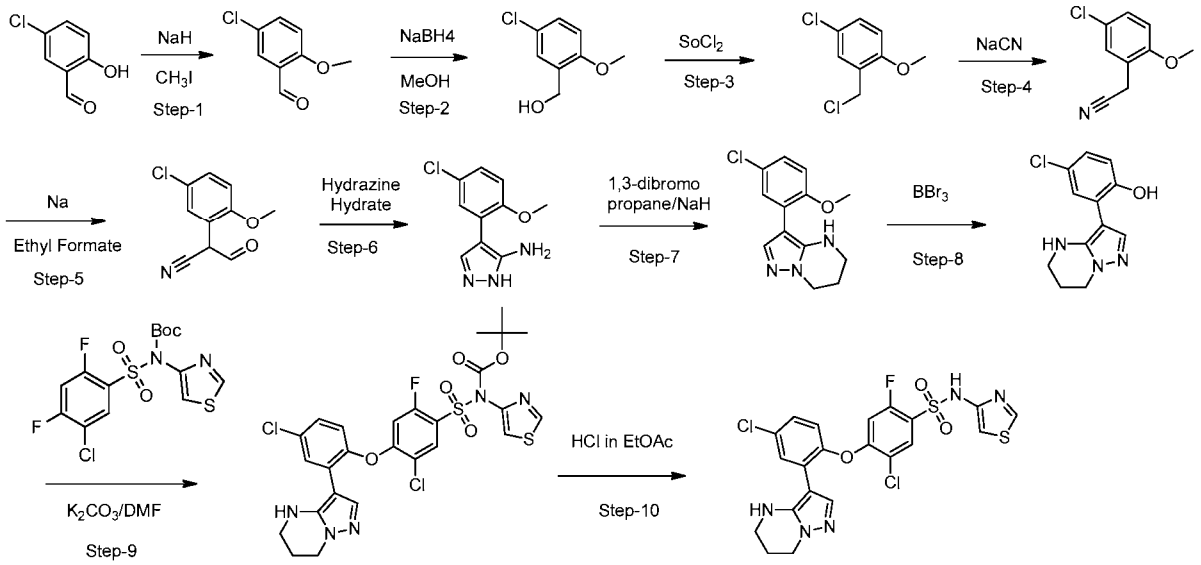
[00390] Compound **31** was synthesized according to the procedure described for the synthesis of compound **11** by replacing glycine methyl ester with 2-(methylsulfonyl)ethanamine in step 2. LC-MS: m/z = 581.8 (M+H). 1H-NMR (MeOD), δ 8.77 (d, *J* = 2.4 Hz,1H), 8.02 (d, *J* = 6.8 Hz, 1H), 7.48 (d, *J* = 2.4 Hz, 1H), 7.36 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 10.4 Hz, 1H), 3.33 – 3.50 (m, 4H), 3.03 (s, 3H), 2.99 – 3.01 (m, 2H), 2.65 – 2.68 (m, 2H), 1.95 – 2.03 (m, 2H).

Example 32: 1-(3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)piperidine-4-carboxylic acid

[00391] Compound **32** was synthesized according to the procedure described for the synthesis of compound **11** by replacing glycine methyl ester with methyl piperidine-4-carboxylate in step 2, and replacing tert-butyl 5-chloro-2,4-difluorophenylsulfonyl(thiazol-4-yl)carbamate with 5-chloro-N-(2,4-dimethoxybenzyl)-2,4-difluoro-N-(1,2,4-thiadiazol-5-yl)benzenesulfonamide in step 4. LC-MS: m/z = 589.6 (M+H).

Example 33: 5-chloro-4-(4-chloro-2-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl)phenoxy)-2-fluoro-N-(thiazol-4-yl)benzenesulfonamide

Scheme 13



[00392] Step 1: Preparation of 5-chloro-2-methoxybenzaldehyde

[00393] A solution of 5-chloro-2-hydroxybenzaldehyde (20g, 128mmol) in DMF (70mL) was cooled to a temperature between 5-10^{0}C. Sodium hydride (7.69g, 192mmol) was added to the above solution in small portions over a period of 20 minutes. Methyl iodide (23.8ml, 384mmol) was then added drop wise to the above reaction mixture whilst maintaining its temperature below 15^{0}C. After completion of addition the reaction mixture was stirred at room temperature for 2 hours. Thereafter the reaction mixture was poured in to cold saturated ammonium chloride solution (250mL) to get white precipitates. The precipitates thus formed were filtered off and dried under vacuo. The resulting solid was triturated with 100 ml of pentane:diethyl ether (4:1) to afford 18g (yield, 82.58%) of the desired compound as a white solid. LC-MS: m/z = 170.1 (M+H).

[00394] Step 2: Preparation of (5-chloro-2-methoxyphenyl) methanol

[00395] A solution of 5-chloro-2-methoxybenzaldehyde (18g, 105.8mmol) in methanol (100mL) was cooled to temperature in between 5-10^{0}C. To the above solution sodium borohydride (11.8g, 317mmol) was added in portion over a period of 30 mins. After completion of addition the resulting reaction mixture was allowed to stir at room temperature for next ~2 hours. The reaction was monitored on TLC using ethyl acetate:hexane (1:1) as mobile phase. After completion of the reaction, it was concentrated under vacuo. To the resulting crude mass, cold water (200 ml) was added to get white precipitate. The precipitate thus formed was filtered and dried to afford 16g (yield, 87.8%) of desired compound as white solid. The material was used directly for the next step.

[00396] Step 3: Preparation of 4-chloro-2-(chloromethyl)-1-methoxybenzene

[00397] A solution of 5-chloro-2-methoxyphenyl)methanol (16g, 94mmol) in DCM (100ml) was cooled to a temperature between 5-10^{0}C. To the above solution thionyl chloride (11ml, 140mmol) was added drop wise over a period of 30 minutes. After completion of addition the resulting reaction mixture was allowed to stir at room temperature for 4 hours. After completion of the reaction, it was concentrated under vacuo. To the resulting crude mass, cold water (150ml) was added to get white precipitates. The precipitate thus formed was filtered off

and dried under vacuo to afford 12g (yield, 67.9%) of the desired compound as a white solid. The material was used directly for the next step.

[00398] Step 4: Preparation of 2-(5-chloro-2-methoxyphenyl)acetonitrile

[00399] To a solution of 4-chloro-2-(chloromethyl)-1-methoxybenzene (12g, 63.15mmol) in DMSO (60mL) was carefully added sodium cyanide (4.4g, 95.6mmol) at room temperature. Above reaction mixture was then heated at 100^0C for 3 hours. After cooling to room temperature, the reaction mixture was poured in to cold water (200mL) to get precipitates. The precipitate thus formed were filtered off and dried under vacuo to afford 10g (yield, 87.46%) of the desired compound as an off white solid. The material was used directly for the next step.

[00400] Step 5: Preparation of 2-(5-chloro-2-methoxyphenyl)-3-oxopropanenitrile

[00401] To a solution of 2-(5-chloro-2-methoxyphenyl)acetonitrile (10g, 47.84mmol) in ethyl formate (50mL) was added sodium metal (4.4g, 95.6mmol) at room temperature. The resulting reaction mixture was heated at 100^0C for 3 hours. After completion of the reaction, it was cooled to room temperature, water (100ml) and dichloromethane (100ml) were added to the reaction mixture and the solution was adjusted to pH-3 with the help of concentrated hydrochloric acid. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 100ml). The combined organics were washed with saturated aqueous sodium chloride solution (150ml), dried over sodium sulphate, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography using normal phase silica gel. The desired product eluted at around 0.7 to 0.9% methanol in dichloromethane. Evaporation of the product fractions gave 9g (yield, 77.94%) of the desired compound as a white solid. LC-MS: m/z = 208.0(M-H).

[00402] Step 6: Preparation of 4-(5-chloro-2-methoxyphenyl)-1H-pyrazol-5-amine

[00403] To a solution of 2-(5-chloro-2-methoxyphenyl)-3-oxopropanenitrile (9g, 43mmol) in ethanol (90mL) was added hydrazine hydrate (4.3g, 86.12mmol) and glacial acetic acid (2.7mL, 51.6mmol) at room temperature. The reaction mixture was then heated under reflux for 3 hours. After completion of the reaction, the reaction mixture was cooled to room temperature and quenched with aqueous sodium bicarbonate (150ml). The resulting mixture was extracted

with dichloromethane (3 x 100ml). The combined organic layers were washed with brine, dried over sodium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography using normal phase silica gel. The desired product eluted at around 0.9 to 1.1% methanol in dichloromethane. Evaporation of the product fractions gave 7g (yield, 72.8%) of the desired compound as a white solid. LC-MS: m/z = 224.1(M+H).

[00404] Step 7: Preparation of 3-(5-chloro-2-methoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine

[00405] A solution of 4-(5-chloro-2-methoxyphenyl)-1H-pyrazol-5-amine (3g, 13.45mmol) in dry DMF (15mL) was cooled to a temperature in between 5-10^{0}C. Sodium hydride (0.806g, 20.17mmol) was added to the above solution in small portions over a period of 30 minutes. The resulting reaction mixture was stirred for 30 minutes at 5-10^{0}C, thereafter 1, 3-dibromopropane (1.78ml, 17.48mmol) was added drop wise to the above mixture. The resulting reaction mixture was heated at 100^{0}C for a period of 4 hrs. After completion of reaction, the solution was diluted with cold water (100mL) and the product was extracted with ethyl acetate (3 x 100). The combined organic layers were washed with brine, dried over sodium sulphate and concentrated *in vacuo*. T he crude product was purified by column chromatography using normal phase silica gel. The desired product eluted at around 1.2 to 1.5% methanol in dichloromethane. Evaporation of the product fractions gave 0.65g (yield, 18.36%) of the desired compound as a semisolid. LC-MS: m/z = 264.2(M+H).

[00406] Step 8: Preparation of 4-chloro-2-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl)phenol

[00407] A solution of 3-(5-chloro-2-methoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine (0.65g, 1.9mmol) in dichloromethane (30mL) was cooled to a temperature between 5-10^{0}C. To the above solution, boron tribromide in dichloromethane (4.7mL, 4.75mmol) was added drop wise over a period of 30 minutes. After completion of addition, the resulting reaction mixture was stirred at room temperature for 4 hours. After completion of reaction, the solution was diluted with cold water (40mL) and the product was extracted with ethyl acetate (3 x 30mL). The combined organic layers were washed with brine, dried over sodium sulphate and

concentrated *in vacuo* to afford 0.65g (yield, 81.24%) of desired compound as white solid. LC-MS: m/z = 250.2(M+H).

[00408] Step 9: Preparation of tert-butyl 5-chloro-4-(4-chloro-2-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl)phenoxy)-2-fluorophenylsulfonyl(thiazol-4-yl)carbamate

[00409] To a solution 4-chloro-2-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl)phenol (0.5g, 2.008mmol) in DMF (8ml) was added K_2CO_3 (0.556g, 4.016mmol) in one portion under nitrogen atmosphere at room temperature. The resulting reaction mixture was stirred at room temperature for 15 minutes. To the above mixture was added tert-butyl 5-chloro-2,4-difluorophenylsulfonyl(thiazol-4-yl)carbamate (0.989g, 2.409mmol) and the resulting reaction mixture was stirred at room temperature for 3 hours. After completion of reaction, water (10ml) was added and the resulting mixture was extracted with ethyl acetate (3 x 25ml). The combined organic extract was washed with water (20ml), brine (20ml), dried over sodium sulphate and concentrated under vacuo. The crude product was purified by column chromatography using normal phase silica gel. The desired product eluted at around 40 to 50% ethyl acetate in hexane. Evaporation of the product fractions gave 0.4g (yield, 31.18%) of the desired compound as a white solid.LC-MS: m/z = 640.1 (M+H).

[00410] Step 10: Preparation of 5-chloro-4-(4-chloro-2-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl)phenoxy)-2-fluoro-N-(thiazol-4-yl)benzenesulfonamide

[00411] To a solution of tert-butyl 5-chloro-4-(4-chloro-2-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl)phenoxy)-2-fluorophenylsulfonyl(thiazol-4-yl)carbamate (0.4g, 0.626mmol) in dichloromethane (15ml) was added drop-wise a 4N solution of hydrochloric acid in ethyl acetate (0.8ml) at room temperature. The resulting reaction mixture was stirred at room temperature for 2 hours. After completion of reaction, pentane (20ml) was added in to the reaction mixture which resulted in precipitation of solid. The solvent layer was decanted off; the solid thus obtained was washed twice with pentane (15ml) and dried under vacuo. The resulting crude material was further purified by Prep HPLC using 0.1% Hydrochloric acid in Water:Acetonitrile mobile phase. Evaporation of the pure product fractions obtained from Prep HPLC provided the desired product as HCl salt (0.130g, 38.6% yield). LC-MS: m/z = 539.78 (M+H). 1H NMR

(400 MHz, Methanol-d4) δ 8.76 (d, J = 2.4 Hz, 1H), 8.02 (s, 1H), 7.95 (d, J = 7.2 Hz, 1H), 7.61 (d, J = 2.4 Hz, 1H), 7.54 (dd, J = 2.4, 8.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 2.0 Hz, 1H), 6.62 (d, J = 10.8 Hz, 1H), 4.14 (t, J = 6.0 Hz, 2H), 3.40 (t, J = 5.6 Hz, 2H), 2.14 (p, J = 6.0 Hz, 2H).

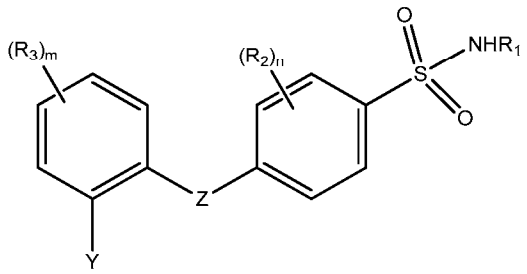
[00412] The embodiments described herein are intended to be merely exemplary, and those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. All such equivalents are considered to be within the scope of the present invention and are covered by the following embodiments.

[00413] All references (including patent applications, patents, and publications) cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (**I**),



Formula (**I**)

or a pharmaceutically acceptable salt, or a stereoisomeric or tautomeric form thereof, wherein:

Z is -O- or -S-;

Y is –X-C(=O)NR_4R_5, –$(CH_2)_3$-NR_9R_{10}, or 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-(2-yl or 3-yl);

X is (C_6-C_{10})aryl or 5- or 6-membered heteroaryl;

R_1 is a partially unsaturated or aromatic 5- or 6-membered heterocycle;

R_2 is independently at each occurrence –F, -Cl, -Br, -CH_3 or -CN;

R_3 is independently at each occurrence –H, -F, -Cl, -Br, -CF_3, -OCF_3, -CN, (C_1-C_{12})alkyl, or (C_1-C_{12})alkoxy;

R_4 and R_5 are each independently H, (C_1-C_9)alkyl, (C_4-C_{12})cycloalkyl, or R_4 and R_5 together form a 5- to 7-membered heterocycloalkyl ring; with the proviso that:

R_4 and R_5 are not both H; and

at least one of R_4 and R_5 independently or said heterocycloalkyl ring formed by R_4 and R_5 together is substituted with 1 or 2 substituents selected from the group consisting of –CO_2H, -CO_2R_6, -CN, -OH, -$CONR_7R_8$, and -NR_7R_8; wherein:

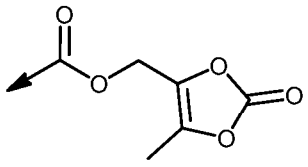
R_6 is (C_1-C_{12})alkyl;

R_7 and R_8 are each independently H, (C_1-C_{12})alkyl, or R_7 and R_8 together form a 4- to 7-membered heterocycloalkyl ring;

R_9 is (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, pyrazolyl or pyridinyl; wherein R_9 is optionally further substituted with 1 or 2 substituents selected from the group consisting

of -COOH, -COOR$_{11}$, -CONR$_{11}$R$_{12}$, -SO$_2$R$_{11}$, -SO$_2$NR$_{11}$R$_{12}$, -OH, -CN, -OR$_{11}$, and -NR$_{11}$R$_{12}$; wherein R$_{11}$ and R$_{12}$ may form a 6 membered heterocycloalkyl ring

R$_{10}$ is R$_{11}$, -COR$_{11}$, -COOR$_{11}$, -SO$_2$R$_{11}$, 5-methyl-2-oxo-1,3-dioxol-4-yl,



, -COO-CH(CH$_3$)OCOCH(CH$_3$)$_2$; or R$_9$ and R$_{10}$ together form a piperazinone or a 4-to 8- membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is substituted with 1 or 2 substituents selected from the group consisting of –COOH, -COOR$_{11}$, -CH$_2$-COOR$_{11}$, -OH, -NH$_2$, -CN, and (C$_1$-C$_8$)alkoxy;

R$_{11}$ and R$_{12}$ are independently H or (C$_1$-C$_6$)alkyl, optionally substituted with 4- to 8-membered heterocycloalkyl ring; and

m and n are each independently 1, 2, 3, or 4.

2. The compound of claim 1, wherein Y is -(CH$_2$)$_3$-NR$_9$R$_{10}$.

3. The compound of claim 2, wherein R$_1$ is an aromatic 5- or 6-membered heterocycle, with 1-3 heteroatoms independently selected from the group consisting of N, O, and S.

4. The compound of any of claims 2 or 3, wherein R$_1$ is pyridyl or pyrimidinyl.

5. The compound of any of claims 2 or 3, wherein R$_1$ is an aromatic 5-membered heterocycle with 1 or 2 nitrogen atoms and optionally 1 or 2 sulphur atoms.

6. The compound of any of claims 2, 3, or 5 wherein R$_1$ is thiazolyl, isothiazolyl, or thiadiazolyl.

7. The compound of any of claims 2, 3, 5, or 6, wherein R$_1$ is thiazolyl.

8. The compound of any of claims 2, 3, 5, or 6, wherein R$_1$ is 1,2,4-thiadiazol-5-yl.

9. The compound of any of claims 2-8, wherein R$_2$ is independently at each occurrence –F or -Cl.

10. The compound of any of claims 2-9, wherein n is 1, 2, or 3.

11. The compound of any of claims 2-10, wherein n is 2.

12. The compound of any of claims 2-11, wherein Z is –O-.

13. The compound of any of claims 2-12, wherein R_3 is independently at each occurrence -H, –F, -Cl, or -Br.

14. The compound of any of claims 2-13, wherein R_3 is –H or –Cl.

15. The compound of any of claims 2-14, wherein R_3 is –Cl.

16. The compound of any of claims 2-15, wherein m is 1, 2, or 3.

17. The compound of any of claims 2-16, wherein m is 1.

18. The compound of any of claims 2-17, wherein R_9 is (C_1-C_6)alkyl; wherein R_9 is optionally further substituted with 1 or 2 substituents selected from the group consisting of -COOH, -COOMe, -$CONH_2$, and –NH_2.

19. The compound of any of claims 2-18, wherein R_9 is methyl or ethyl.

20. The compound of any of claims 2-19, wherein R_9 is further substituted with -COOH.

21. The compound of any of claims 2-20, wherein R_{10} is –H, –COMe, -COOEt.

22. The compound of any of claims 2-20, wherein R_{10} is -H or –COMe.

23. The compound of any of claims 2-22, wherein R_{10} is -H.

24. The compound of any of claims 2-17, wherein R_9 and R_{10} together form a 4 to 8 membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is substituted with 1 or 2 groups selected from the group consisting of –COOH, –COOMe, –COOEt, -CH_2-COOH, and -NH_2.

25. The compound of any of claims 2-17, wherein R_9 and R_{10} together form a 4 to 8 membered heterocycloalkyl ring, wherein said heterocycloalkyl ring is substituted with 1 or 2 groups selected from the group consisting of –COOH, -CH_2-COOH, and -NH_2.

26. The compound of any of claims 2-17, wherein R_9 and R_{10} together form a piperidine substituted with 1 or 2 groups selected from the group consisting of –COOH, –COOMe, –COOEt, -CH_2-COOH, -CH_2-COOMe, -CH_2-COOEt, and -NH_2.

27. The compound of any of claims 2-17, wherein R_9 and R_{10} together form a piperidine substituted with 1 or 2 groups selected from the group consisting of –COOH, -CH_2-COOH, and -NH_2.

28. The compound of claim 1, wherein Y is –X-C(=O)NR_4R_5.

29. The compound of claim 28, wherein R_1 is an aromatic 5- or 6-membered heterocycle, with 1-3 heteroatoms independently selected from the group consisting of N, O, and S.

30. The compound of any of claims 28 or 29, wherein R_1 is pyridyl or pyrimidinyl.

31. The compound of any of claims 28 or 29, wherein R_1 is an aromatic 5-membered heterocycle with 1 or 2 nitrogen atoms and optionally 1 or 2 sulphur atoms.

32. The compound of any of claims 28, 29, or 31 wherein R_1 is thiazolyl, isothiazolyl, or thiadiazolyl.

33. The compound of any of claims 28, 29, 31, or 32, wherein R_1 is thiazolyl.

34. The compound of any of claims 28, 29, 31, or 32, wherein R_1 is 1,2,4-thiadiazol-5-yl.

35. The compound of any of claims 28-34, wherein R_2 is independently at each occurrence -F or -Cl.

36. The compound of any of claims 28-35, wherein n is 1, 2, or 3.

37. The compound of any of claims 28-36, wherein n is 2.

38. The compound of any of claims 28-37, wherein Z is –O-.

39. The compound of any of claims 28-38, wherein R_3 is independently at each occurrence -F, -Cl, or -Br.

40. The compound of any of claims 28-39, wherein R_3 is –H or –Cl.

41. The compound of any of claims 28-40, wherein R_3 is –Cl.

42. The compound of any of claims 28-41, wherein m is 1, 2, or 3.

43. The compound of any of claims 28-42, wherein m is 1.

44. The compound of any of claims 28-43, wherein X is 5- or 6-membered heteroaryl.

45. The compound of any of claims 28-44, wherein X is pyridyl or pyrimidinyl.

46. The compound of any of claims 28-45, wherein X is pyridyl.

47. The compound of any of claims 28-46, wherein R_4 is H and R_5 is $(C_1\text{-}C_9)$alkyl.

48. The compound of any of claims 28-47, wherein R_5 is methyl or ethyl, substituted with 1 or 2 substituents selected from the group consisting of $-CO_2H$, $-CO_2R_6$, and $-CONR_7R_8$.

49. The compound of any of claims 28-48, wherein R_6 is $(C_1\text{-}C_6)$alkyl.

50. The compound of any of claims 28-48, wherein R_5 is methyl or ethyl, substituted with $-CO_2H$.

51. The compound of claim 1, wherein Y is 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-(2-yl or 3-yl).

52. The compound of claim 51, wherein Y is 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-yl.

53. The compound of any of claims 51 or 52, wherein R_1 is an aromatic 5- or 6-membered heterocycle, with 1-3 heteroatoms independently selected from the group consisting of N, O, and S.

54. The compound of any of claims 51-53, wherein R_1 is pyridyl or pyrimidinyl.

55. The compound of any of claims 51-53, wherein R_1 is an aromatic 5-membered heterocycle with 1 or 2 nitrogen atoms and optionally 1 or 2 sulphur atoms.

56. The compound of any of claims 51-53, or 55 wherein R_1 is thiazolyl, isothiazolyl, or thiadiazolyl.

57. The compound of any of claims 51-53, 55, or 56, wherein R_1 is thiazolyl.

58. The compound of any of claims 51-53, 55, or 56, wherein R_1 is 1,2,4-thiadiazol-5-yl.

59. The compound of any of claims 51-58, wherein R_2 is independently at each occurrence -F or -Cl.

60. The compound of any of claims 51-59, wherein n is 1, 2, or 3.

61. The compound of any of claims 51-60, wherein n is 2.

62. The compound of any of claims 51-61, wherein Z is –O-.

63. The compound of any of claims 51-62, wherein R_3 is independently at each occurrence -F, -Cl, or -Br.

64. The compound of any of claims 51-63, wherein R_3 is –H or –Cl.

65. The compound of any of claims 51-64, wherein R_3 is –Cl.

66. The compound of any of claims 51-65, wherein m is 1, 2, or 3.

67. The compound of any of claims 51-66, wherein m is 1.

68. The compound of claim 1, wherein the compound is
3-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid,
2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)acetic acid,
5-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)pentanoic acid,
4-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)butanoic acid,
2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid,
(R)-2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid,
2-(6-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)acetic acid,
(S)-2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid,
3-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-cyanophenoxy)-5-chlorophenyl)picolinamido)propanoic acid,
3-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2,5-difluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid,
2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid,
3-((3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)amino)propanoic acid,
2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid,
1-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)piperidine-4-carboxylic acid,
3-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid,

4-amino-1-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)piperidine-4-carboxylic acid,
2-amino-4-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)butanoic acid,
2-((3-(5-chloro-2-(2,5-difluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid,
1-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)piperidine-3-carboxylic acid,
2-((3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)phenyl)propyl)amino)acetic acid,
2-((3-(5-chloro-2-(2,5-difluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetic acid,
3-((3-(5-chloro-2-(2,5-difluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid,
3-((3-(5-chloro-2-(2-cyano-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid,
methyl 2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)acetate,
3-((3-(2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)-5-fluorophenyl)propyl)amino)propanoic acid,
3-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanamide,
2-(N-(3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)acetamido)acetic acid,
2-(1-(3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)piperidin-4-yl)acetic acid,
3-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-2-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)propanoic acid,
2-((3-(5-chloro-2-(2-chloro-5-fluoro-4-(N-(thiazol-4-yl)sulfamoyl)phenoxy)phenyl)propyl)amino)-N-methylacetamide,
5-chloro-4-(4-chloro-2-(3-((2-(methylsulfonyl)ethyl)amino)propyl)phenoxy)-2-fluoro-N-

(thiazol-4-yl)benzenesulfonamide,
1-(3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)piperidine-4-carboxylic acid, or
5-chloro-4-(4-chloro-2-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-3-yl)phenoxy)-2-fluoro-N-(thiazol-4-yl)benzenesulfonamide
or a pharmaceutically acceptable salt, or a stereoisomeric or tautomeric form thereof.

69. The compound of any of claims 1 or 68, wherein the compound is
2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)acetic acid,
3-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid,
2-(4-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)picolinamido)propanoic acid, or
3-((3-(2-(4-(N-(1,2,4-thiadiazol-5-yl)sulfamoyl)-2-chloro-5-fluorophenoxy)-5-chlorophenyl)propyl)amino)propanoic acid;
or a pharmaceutically acceptable salt, or a stereoisomeric or tautomeric form thereof.

70. A method for treating neuropathic pain comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate or tautomeric form thereof.

71. A method for treating pain comprising use of a compound of Formula (I), as a voltage-gated sodium channel inhibitor.

72. The method of claim 71, wherein the pain is neuropathic, nociceptive or inflammatory pain.

73. The method of claim 71, wherein the voltage-gated sodium channel is NaV1.7.

74. A pharmaceutical composition comprising a compound of any one of claims 1 to 69 and a pharmaceutically acceptable carrier.

75. The composition of claim 74, wherein the composition is suitable for topical, oral, subcutaneous, or intravenous administration.

76. A method for prevention or treatment of pain in a subject, wherein the method comprises administering to the subject in need of such prevention or treatment a therapeutically effective amount of a compound of any one of claims 1 to 69.

77. The method of claim 76, wherein the therapeutically effective amount is effective to alleviate pain in a subject, wherein the compound of any one of claims 1 to 69 shows a reduction in pain response in the Formalin Assay in phase 1 or phase 2, or both, at a dose between 0.1 mg/kg and 1,000 mg/kg, at a dose between 0.5 mg/kg and 100 mg/kg, or at a dose between 1 mg/kg to 50 mg/kg.

78. The method of claim 76, wherein the pain is nociceptive pain, such as that resulting from physical trauma (e.g., a cut or contusion of the skin; or a chemical or thermal burn), osteoarthritis, rheumatoid arthritis or tendonitis; myofascial pain; neuropathic pain, such as that associated with stroke, diabetic neuropathy, luetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, fibromyalgia, or painful neuropathy induced iatrogenically by drugs; or mixed pain (i.e., pain with both nociceptive and neuropathic components); visceral pain; headache pain (e.g., migraine headache pain); CRPS; CRPS type I; CRPS type II; RSD; reflex neurovascular dystrophy; reflex dystrophy; sympathetically maintained pain syndrome; causalgia; Sudeck atrophy of bone; algoneurodystrophy; shoulder hand syndrome; post-traumatic dystrophy; autonomic dysfunction; autoimmune-related pain; inflammation-related pain; cancer-related pain; phantom limb pain; chronic fatigue syndrome; post-operative pain; spinal cord injury pain; central post-stroke pain; radiculopathy; sensitivity to temperature, light touch or color change to the skin (allodynia); pain from hyperthermic or hypothermic conditions; and other painful conditions (e.g., diabetic neuropathy, luetic neuropathy, postherpetic neuralgia, trigeminal neuralgia); chronic pain; or acute pain.

79. A method for modulating the activity of a voltage-gated sodium channel, wherein the method comprises contacting a cell that expresses the voltage-gated sodium channel with a compound of any one of claims 1 to 69.

80. The method of claim 79, wherein the voltage-gated sodium channel is NaV1.7.

81. The method of claim 79, wherein the method results in inhibition of the voltage-gated sodium channel.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/25809

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/18; A61P 29/00 (2014.01)
USPC - 514/601; 514/602; 514/557; 514/604; 514/717; 514/721
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/601; 514/602
IPC(8): A61K 31/18; A61P 29/00 (2014.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/557; 514/604; 514/717; 514/721 (See Search Words Below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PATBASE: Full-text = AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO
Google: Scholar/Patents: bicyclic ether sulfonamide thiazole ion channel NaV1.7 benzenesulfonamide pyrimidine picolinamide proprionic acetic acid neuropathic pain tetrahydro pyrazolo[1,5-a]pyrimidine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2012/004706 A2 (MARKWORTH et al.) 12 January 2012 (12.01.2012) pg 3, ln 25-29; pg 31, Example 2 ; pg 17, ln 1-24; pg 36, example 6	1-5; 28-31; 51-53; 68-73
Y	US 2008/0312235 A1 (LANE et al.) 18 December 2008 (18.12.2008) para [0003];[0222]	1-5; 28-31; 51-53; 68-73
Y	US 2012/0010207 A1 (BELL et al.) 12 January 2012 (12.01.2012) para [0035]-[0037];[0040];[0153];[0176]	2-5
Y	US 2004/0127508 A1 (GERLACH et al.) 01 July 2004 (01.07.2004) para [0008];[0279];[0282]	51-53
Y	US 2009/0023740 A1 (FULP et al.) 22 January 2009 (22.01.2009) para [0225]-[0227]	68-69

☐ Further documents are listed in the continuation of Box C. ☐

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

Date of the actual completion of the international search	Date of mailing of the international search report
09 June 2014 (09.06.2014)	07 JUL 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/25809

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

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

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

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

3. ☒ Claims Nos.: 6-27, 32-50, 54-67 and 74-81
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

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

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

(19)中华人民共和国国家知识产权局

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A61K 31/18(2006.01)
A61P 29/00(2006.01)

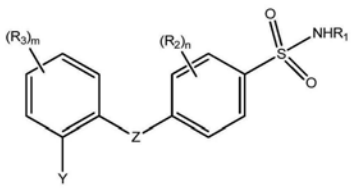
权利要求书7页 说明书68页

(54)发明名称

用于治疗疼痛的钠通道调节剂

(57)摘要

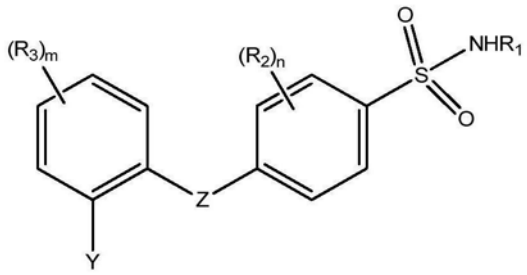
本发明提供了钠通道调节化合物，特别是式(I)的NaV1.7调节化合物。具体地，本发明提供了制备这种化合物的方法、在制备这种化合物中使用的中间产物、包括这种化合物的药物组合物以及包括施用这种化合物的治疗方法。尤其是，本发明提供了用于治疗疼痛的化合物。



式(I)

CN 105188694 A

1.一种式(I)的化合物,



式(I)

或其可药用的盐、或其立体异构形式或互变异构形式,其中:

Z是-O-或-S-;

Y是-X-C(=O)NR_4R_5、$-(CH_2)_3-NR_9R_{10}$、或4,5,6,7-四氢吡唑并[1,5-α]嘧啶-(2-基或3-基);

X是(C_6-C_{10})芳基或5元杂芳基或6元杂芳基;

R_1是部分未饱和的或芳香族的5元杂环或6元杂环;

R_2在每次出现时独立地为-F、-Cl、-Br、$-CH_3$或-CN;

R_3在每次出现时独立地为-H、-F、-Cl、-Br、$-CF_3$、-OCF3、-CN、(C_1-C_{12})烷基、或(C_1-C_{12})烷氧基;

R_4和R_5均独立地为H、(C_1-C_9)烷基、(C_4-C_{12})环烷基,或者R_4和R_5一起形成5至7元杂环烷基环;前提条件是:

R_4和R_5都不是H;并且

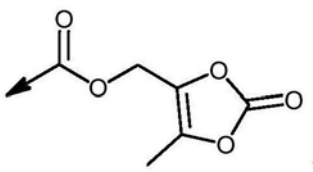
R_4和R_5中至少一个独立地被或R_4和R_5一起形成的所述杂环烷基环被选自由$-CO_2H$、$-CO_2R_6$、-CN、-OH、$-CONR_7R_8$和$-NR_7R_8$组成的组中的1或2个取代基取代;其中:

R_6是(C_1-C_{12})烷基;

R_7和R_8均独立地为H、(C_1-C_{12})烷基,或R_7和R_8一起形成4至7元杂环烷基环;

R_9是(C_1-C_6)烷基、(C_3-C_8)环烷基、吡唑基或吡啶基;其中,R_9可任选地进一步被选自由-COOH、$-COOR_{11}$、$-CONR_{11}R_{12}$、$-SO_2R_{11}$、$-SO_2NR_{11}R_{12}$、-OH、-CN、$-OR_{11}$和$-NR_{11}R_{12}$组成的组中的1或2个取代基取代;其中,R_{11}和R_{12}可以形成6元杂环烷基环;

R_{10}是R_{11}、$-COR_{11}$、$-COOR_{11}$、$-SO_2R_{11}$、5-甲基-2-氧代-1,3-二氧杂环戊烯-4-基、



$-COO-CH(CH_3)OCOCH(CH_3)_2$;或$R_9$和$R_{10}$一起形成哌嗪酮或4至8元杂环烷基环,其中所述杂环烷基环被选自由-COOH、$-COOR_{11}$、$-CH_2-COOR_{11}$、-OH、$-NH_2$、-CN、和(C_1-C_8)烷氧基组成的组中的1或2个取代基取代;

R_{11}和R_{12}独立地为H或(C_1-C_6)烷基,任选地被4至8元杂环烷基环取代;并且

m和n均独立地为1、2、3或4。

2.根据权利要求1所述的化合物,其中,Y是$-(CH_2)_3-NR_9R_{10}$。

3.根据权利要求2所述的化合物,其中,R_1是具有独立地选自由N、O、和S组成的组中

的 1-3 个杂原子的芳香族 5 元杂环或 6 元杂环。

4. 根据权利要求 2 或 3 中任一项所述的化合物，其中，R_1是吡啶基或嘧啶基。

5. 根据权利要求 2 或 3 中任一项所述的化合物，其中，R_1是具有 1 或 2 个氮原子且任选地具有 1 或 2 个硫原子的芳香族 5 元杂环。

6. 根据权利要求 2、3 或 5 中任一项所述的化合物，其中，R_1是噻唑基、异噻唑基或噻二唑基。

7. 根据权利要求 2、3、5 或 6 中任一项所述的化合物，其中，R_1是噻唑基。

8. 根据权利要求 2、3、5 或 6 中任一项所述的化合物，其中，R_1是 1,2,4- 噻二唑 -5- 基。

9. 根据权利要求 2-8 中任一项所述的化合物，其中，R_2在每次出现时独立地为 -F 或 -Cl。

10. 根据权利要求 2-9 中任一项所述的化合物，其中，n 是 1、2 或 3。

11. 根据权利要求 2-10 中任一项所述的化合物，其中，n 是 2。

12. 根据权利要求 2-11 中任一项所述的化合物，其中，Z 是 -O-。

13. 根据权利要求 2-12 中任一项所述的化合物，其中，R_3在每次出现时独立地为 -H、-F、-Cl 或 -Br。

14. 根据权利要求 2-13 中任一项所述的化合物，其中，R_3是 -H 或 -Cl。

15. 根据权利要求 2-14 中任一项所述的化合物，其中，R_3是 -Cl。

16. 根据权利要求 2-15 中任一项所述的化合物，其中，m 是 1、2 或 3。

17. 根据权利要求 2-16 中任一项所述的化合物，其中，m 是 1。

18. 根据权利要求 2-17 中任一项所述的化合物，其中，R_9为 (C_1-C_6) 烷基；其中 R_9任选地进一步被选自由 -COOH、-COOMe、-$CONH_2$、和 -NH_2组成的组中的 1 或 2 个取代基取代。

19. 根据权利要求 2-18 中任一项所述的化合物，其中，R_9是甲基或乙基。

20. 根据权利要求 2-19 中任一项所述的化合物，其中，R_9进一步被 -COOH 取代。

21. 根据权利要求 2-20 中任一项所述的化合物，其中，R_{10}是 -H、-COMe、-COOEt。

22. 根据权利要求 2-20 中任一项所述的化合物，其中，R_{10}是 -H 或 COMe。

23. 根据权利要求 2-22 中任一项所述的化合物，其中，R_{10}是 -H。

24. 根据权利要求 2-17 中任一项所述的化合物，其中，R_9和 R_{10}一起形成 4 至 8 元杂环烷基环，其中所述杂环烷基环被选自由 -COOH、-COOMe、-COOEt、-CH_2-COOH 和 -NH_2组成的组中的 1 或 2 个基团取代。

25. 根据权利要求 2-17 中任一项所述的化合物，其中，R_9和 R_{10}一起形成 4 至 8 元杂环烷基环，其中所述杂环烷基环被选自由 -COOH、-CH_2-COOH 和 -NH_2组成的组中的 1 或 2 个基团取代。

26. 根据权利要求 2-17 中任一项所述的化合物，其中，R_9和 R_{10}一起形成被选自由 -COOH、-COOMe、-COOEt、-CH_2-COOH、-CH_2-COOMe、-CH_2-COOEt 和 -NH_2组成的组中的 1 或 2 个基团取代的哌啶。

27. 根据权利要求 2-17 中任一项所述的化合物，其中，R_9和 R_{10}一起形成被选自由 -COOH、-CH_2-COOH 和 -NH_2组成的组中的 1 或 2 个基团取代的哌啶。

28. 根据权利要求 1 所述的化合物，其中，Y 是 -X-C(= O)NR_4R_5。

29. 根据权利要求 28 所述的化合物，其中，R_1是具有独立地选自由 N、O、和 S 组成的组

中的 1-3 个杂原子的芳香族 5 元杂环或 6 元杂环。

30. 根据权利要求 28 或 29 中任一项所述的化合物，其中，R_1是吡啶基或嘧啶基。

31. 根据权利要求 28 或 29 中任一项所述的化合物，其中，R_1是具有 1 或 2 个氮原子并且可选地具有 1 或 2 个硫原子的芳香 5 元杂环。

32. 根据权利要求 28、29 或 31 中任一项所述的化合物，其中，R_1是噻唑基、异噻唑基或噻二唑基。

33. 根据权利要求 28、29、31 或 32 中任一项所述的化合物，其中，R_1是噻唑基。

34. 根据权利要求 28、29、31 或 32 中任一项所述的化合物，其中，R_1是 1,2,4- 噻二唑 -5- 基。

35. 根据权利要求 28-34 中任一项所述的化合物，其中，R_2在每次出现时独立为 -F 或 -Cl。

36. 根据权利要求 28-35 中任一项所述的化合物，其中，n 是 1、2 或 3。

37. 根据权利要求 28-36 中任一项所述的化合物，其中，n 是 2。

38. 根据权利要求 28-37 中任一项所述的化合物，其中，Z 是 -O-。

39. 根据权利要求 28-38 中任一项所述的化合物，其中，R_3在每次出现时独立为 -F、-Cl 或 -Br。

40. 根据权利要求 28-39 中任一项所述的化合物，其中，R_3是 -H 或 -Cl。

41. 根据权利要求 28-40 中任一项所述的化合物，其中，R_3是 -Cl。

42. 根据权利要求 28-41 中任一项所述的化合物，其中，m 是 1、2 或 3。

43. 根据权利要求 28-42 中任一项所述的化合物，其中，m 是 1。

44. 根据权利要求 28-43 中任一项所述的化合物，其中，X 是 5 元杂芳基或 6 元杂芳基。

45. 根据权利要求 28-44 中任一项所述的化合物，其中，X 是吡啶基或嘧啶基。

46. 根据权利要求 28-45 中任一项所述的化合物，其中，X 是吡啶基。

47. 根据权利要求 28-46 中任一项所述的化合物，其中，R_4是 H 并且 R_5是 (C_1-C_9) 烷基。

48. 根据权利要求 28-47 中任一项所述的化合物，其中，R_5是被选自由 $-CO_2H$、$-CO_2R_6$ 和 $-CONR_7R_8$组成的组中的 1 或 2 个取代基取代的甲基或乙基。

49. 根据权利要求 28-48 中任一项所述的化合物，其中，R_6是 (C_1-C_6) 烷基。

50. 根据权利要求 28-48 中任一项所述的化合物，其中，R_5是被 $-CO_2H$ 取代的甲基或乙基。

51. 根据权利要求 1 所述的化合物，其中，Y 为 4,5,6,7- 四氢吡唑并 [1,5-α] 嘧啶 -(2- 基或 3- 基)。

52. 根据权利要求 51 所述的化合物，其中，Y 为 4,5,6,7- 四氢吡唑并 [1,5-α] 嘧啶 -3- 基。

53. 根据权利要求 51 或 52 中任一项所述的化合物，其中，R_1是具有独立地选自由 N、O、和 S 组成的组中的 1-3 个杂原子的芳香族 5 元杂环或 6 元杂环。

54. 根据权利要求 51-53 中任一项所述的化合物，其中，R_1是吡啶基或嘧啶基。

55. 根据权利要求 51-53 中任一项所述的化合物，其中，R_1是具有 1 或 2 个氮原子并且可选地具有 1 或 2 个硫原子的芳香族 5 元杂环。

56. 根据权利要求 51-53 或 55 中任一项所述的化合物，其中，R_1是噻唑基、异噻唑基或

噻二唑基。

57.根据权利要求51-53、55或56中任一项所述的化合物，其中，R_1是噻唑基。

58.根据权利要求51-53、55或56中任一项所述的化合物，其中，R_1是1,2,4-噻二唑-5-基。

59.根据权利要求51-58中任一项所述的化合物，其中，R_2在每次出现时独立地为-F或-Cl。

60.根据权利要求51-59中任一项所述的化合物，其中，n是1、2或3。

61.根据权利要求51-60中任一项所述的化合物，其中，n是2。

62.根据权利要求51-61中任一项所述的化合物，其中，Z是-O-。

63.根据权利要求51-62中任一项所述的化合物，其中，R_3在每次出现时独立地为-F、-Cl或-Br。

64.根据权利要求51-63中任一项所述的化合物，其中，R_3是-H或-Cl。

65.根据权利要求51-64中任一项所述的化合物，其中，R_3是-Cl。

66.根据权利要求51-65中任一项所述的化合物，其中，m是1、2或3。

67.根据权利要求51-66中任一项所述的化合物，其中，m是1。

68.根据权利要求1所述的化合物，其中，所述化合物是：

3-(4-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)吡啶酰胺基)丙酸、

2-(4-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)吡啶酰胺基)乙酸、

5-(4-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)吡啶酰胺基)戊酸、

4-(4-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)吡啶酰胺基)丁酸、

2-(4-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)吡啶酰胺基)丙酸、

(R)-2-(4-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)吡啶酰胺基)丙酸、

2-(6-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)吡啶酰胺基)乙酸、

(S)-2-(4-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)吡啶酰胺基)丙酸、

3-(4-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氰基苯氧基)-5-氯苯基)吡啶酰胺基)丙酸、

3-(4-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2,5-二氟苯氧基)-5-氯苯基)吡啶酰胺基)丙酸、

2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)乙酸、

3-((3-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯

基）丙基）氨基）丙酸、

2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-2-基）氨磺酰基）苯氧基）苯基）丙基）氨基）乙酸、

1-(3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）哌啶)-4-羧酸、

3-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）氨基）丙酸、

4-氨基-1-(3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）哌啶)-4-羧酸、

2-氨基-4-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）氨基）丁酸、

2-((3-(5-氯-2-(2,5-二氟-4-(N-(噻唑-2-基）氨磺酰基）苯氧基）苯基）丙基）氨基）乙酸、

1-(3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）哌啶)-3-羧酸、

2-((3-(2-(4-(N-(1,2,4-噻二唑-5-基）氨磺酰基)-2-氯-5-氟苯氧基）苯基）丙基）氨基）乙酸、

2-((3-(5-氯-2-(2,5-二氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）氨基）乙酸、

3-((3-(5-氯-2-(2,5-二氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）氨基）丙酸、

3-((3-(5-氯-2-(2-氰基-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）氨基）丙酸、

甲基2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）氨基）乙酸酯、

3-((3-(2-(2-氯-5-氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基)-5-氟苯基）丙基）氨基）丙酸、

3-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）氨基）丙酰胺、

2-(N-(3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）乙酰氨基）乙酸、

2-(1-(3-(2-(4-(N-(1,2,4-噻二唑-5-基）氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基）丙基）哌啶-4-基）乙酸、

3-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-2-基）氨磺酰基）苯氧基）苯基）丙基）氨基）丙酸、

2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）氨基)-N-甲基乙酰胺、

5-氯-4-(4-氯-2-(3-((2-(甲磺酰基）乙基）氨基）丙基）苯氧基)-2-氟-N-(噻唑-4-基）苯磺酰胺、

1-(3-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)丙基)哌啶-4-羧酸、或

5-氯-4-(4-氯-2-(4,5,6,7-四氢吡唑并[1,5-α]嘧啶-3-基)苯氧基)-2-氟-N-(噻唑-4-基)苯磺酰胺、

或其可药用的盐、或其立体异构形式或互变异构形式。

69.根据权利要求1或68的任一项所述的化合物,其中所述化合物是:

2-(4-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)吡啶酰胺基)乙酸、

3-(4-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)吡啶酰胺基)丙酸、

2-(4-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)吡啶酰胺基)丙酸、或

3-((3-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)丙基)氨基)丙酸;

或可药用的盐,或它的立体异构形式或互变异构形式。

70.一种用于治疗神经性疼痛的方法,包括将治疗有效量的式(I)的化合物,或治疗有效量的该化合物的盐或溶剂化物或互变异构形式给药于有此需要的受试者。

71.一种用于治疗疼痛的方法,包括使用式(I)的化合物作为电压依赖性钠通道抑制剂。

72.根据权利要求71所述的方法,其中,所述疼痛为神经性疼痛、伤害性疼痛或炎性疼痛。

73.根据权利要求71所述的方法,其中,所述电压依赖性钠通道为NaV1.7。

74.一种药物组合物,包括根据权利要求1-69中任一项所述的化合物和可药用的载体。

75.根据权利要求74所述的组合物,其中,所述组合物适用于局部给药、口服给药、皮下注射给药或静脉给药。

76.一种用于预防或治疗受试者中的疼痛的方法,其中,所述方法包括将治疗有效量的根据权利要求1-69中任一项所述的化合物给药于需要这种预防或治疗的受试者。

77.根据权利要求76所述的方法,其中,所述治疗有效量是对减轻受试者中的疼痛有效,其中根据权利要求1-69中任一项所述的化合物以0.1mg/kg至1000mg/kg的剂量、以0.5mg/kg至100mg/kg的剂量或以1mg/kg至50mg/kg的剂量在福尔马林试验的阶段1或阶段2或两个阶段中表现出减小疼痛反应。

78.根据权利要求76所述的方法,其中,所述疼痛是伤害性疼痛如由物理创伤导致的疼痛(例如,皮肤的切口或挫伤;或化学烧伤或热烧伤)、骨关节炎、类风湿性关节炎或肌腱炎;肌筋膜疼痛;神经性疼痛如与中风、糖尿病性神经病、梅毒性神经病、带状疱疹后神经痛、三叉神经痛、纤维肌痛、或由药物医源性地诱导的疼痛性神经病相关的神经性疼痛;或混合型疼痛(即,具有伤害性和神经性成分的疼痛);内脏疼痛;头痛(例如,偏头痛);CRPS;CRPS I型;CRPS II型;RSD;反射性神经血管营养不良;反射性营养不良;交感神经维持疼痛综合征;灼痛;祖德克骨萎缩;痛觉神经营养不良;肩手综合征;创伤后营养不良;

自主机能障碍；自身免疫相关的疼痛；炎症相关的疼痛；癌症相关的疼痛；幻肢痛；慢性疲劳综合征；手术后的疼痛；脊髓损伤性疼痛；卒中后中枢痛；神经根病；对皮肤的温度、轻触或颜色变化的敏感性（痛觉超敏）；源于高热或低热病症的疼痛；和其它疼痛病症（例如，糖尿病性神经病、梅毒性神经病、带状疱疹后神经痛、三叉神经痛）；慢性疼痛；或急性疼痛。

79. 一种用于调控电压依赖性钠通道的活性的方法，其中，所述方法包括使表达电压依赖性钠通道的细胞与根据权利要求 1-69 中任一项所述的化合物接触。

80. 根据权利要求 79 所述的方法，其中，所述电压依赖性钠通道为 NaV1.7。

81. 根据权利要求 79 所述的方法，其中，所述方法导致抑制电压依赖性钠通道。

用于治疗疼痛的钠通道调节剂

[0001] 本申请主张于 2013 年 3 月 15 日提交的美国临时申请第 61/787,618 号的权益，该美国临时申请的内容通过引用的方式全部并入本文中。

技术领域

[0002] 本发明提供了钠通道调节化合物，特别是 NaV1.7 调节化合物。具体地，本发明提供了制备所述化合物的方法、在制备所述化合物中使用的中间产物、包括所述化合物的药物组合物以及包括施用所述化合物的治疗方法。具体地，本发明提供了用于治疗疼痛的化合物。

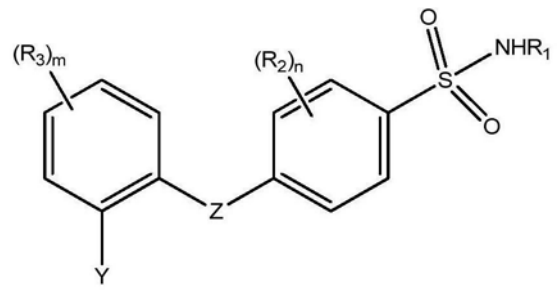
背景技术

[0003] 电压依赖性离子通道在神经元和肌肉细胞的电活动中发挥着关键作用。已经辨别出许多种类的电压依赖性离子通道（例如，钠通道）。由于它们在各种病理学条件的潜在作用，这些离子通道已经是重要药理学研究的对象。生物物理学和药理学研究已经确定钠通道亚型 NaV1.3、NaV1.7、NaV1.8、和 NaV1.9 在疼痛，尤其是神经性疼痛的病理生理学中尤为重要。最近，SCN9A（一种编码 NaV1.7 的基因）中的功能获得突变与两种人类遗传性疼痛综合症、遗传性红斑性肢痛症和阵发性剧痛症有关联，然而 SCN9A 中的功能缺失突变与对疼痛完全不敏感有关联 (Dib-Hajj 等人，Pain Medicine（疼痛医学）10(7)：1260-1269(2009)（摘要））。疼痛症状影响将近 1 亿美国成年人，每年直接医疗费用和损失的生产力为 5600-6350 亿美元 (Relieving Pain in America（缓解美国人的疼痛），National Academies Press（国家科学出版社），Washington（华盛顿），DC(2011)，第 2 页）。遗憾的是，当前的治疗选择典型地仅提供部分疼痛缓解，并且受限于不便加药和副作用，如嗜睡、运动失调、水肿、肠胃不适和呼吸抑制。因此，需要新型化合物来解决目前可用的治疗选择的缺点。

发明内容

[0004] 本文提供了式 (I) 的化合物，

[0005]



式（I）

[0006] 或可药用的盐、或其立体异构形式或互变异构形式，其中：

[0007] Z 是 -O- 或 -S- ；

[0008] Y 是 -X-C(= O)NR_4R_5、-$(CH_2)_3$-NR_9R_{10}、或 4,5,6,7- 四氢吡唑并[1,5-α]嘧啶 -(2- 基或 3- 基)；

[0009] X 是 (C_6-C_{10}) 芳基或 5 元杂芳基或 6 元杂芳基；

[0010] R_1是部分未饱的和或芳香族的 5 元杂环或 6 元杂环；

[0011] R_2在每次出现时独立地为 -F、-Cl、-Br、-CH_3或 -CN；

[0012] R_3在每次出现时独立地为 -H、-F、-Cl、-Br、-CF_3、-OCF_3、-CN、(C_1-C_{12}) 烷基、或 (C_1-C_{12}) 烷氧基；

[0013] R_4和 R_5均独立地为 H、(C_1-C_9) 烷基、(C_4-C_{12}) 环烷基或 R_4和 R_5一起形成 5 至 7 元杂环烷基环；前提条件是：

[0014] R_4和 R_5都不是 H；并且

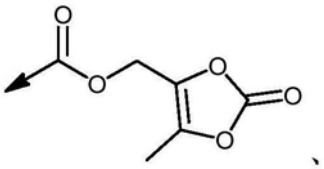
[0015] R_4和 R_5中至少一个独立地被或 R_4和 R_5一起形成的所述杂环烷基环被选自由 -CO_2H、-CO_2R_6、-CN、-OH、-$CONR_7R_8$和 -NR_7R_8组成的组中的 1 或 2 个取代基取代；其中：

[0016] R_6是 (C_1-C_{12}) 烷基；

[0017] R_7和 R_8各自独立地为 H、(C_1-C_{12}) 烷基，或 R_7和 R_8一起形成 4 至 7 元杂环烷基环；

[0018] R_9是 (C_1-C_6) 烷基、(C_3-C_8) 环烷基、吡唑基或吡啶基；其中，R_9任选地进一步被选自由 -COOH、-$COOR_{11}$、-$CONR_{11}R_{12}$、-SO_2R_{11}、-$SO_2NR_{11}R_{12}$、-OH、-CN、-OR_{11}和 -$NR_{11}R_{12}$组成的组中的 1 或 2 个取代基取代；其中，R_{11}和 R_{12}可以形成 6 元杂环烷基环；

[0019] R_{10}是 R_{11}、-COR_{11}、-$COOR_{11}$、-SO_2R_{11}、5- 甲基 -2- 氧代 -1,3- 二氧杂环戊烯 -4- 基、



-COO-$CH(CH_3)OCOCH(CH_3)_2$；或 R_9和 R_{10}一起形成哌嗪酮或 4 至 8 元杂环烷基环，其中所述杂环烷基环被选自由 -COOH、-$COOR_{11}$、-CH_2-$COOR_{11}$、-OH、-NH_2、-CN 和 (C_1-C_8) 烷氧基组成的组中的 1 或 2 个取代基取代；

[0020] R_{11}和 R_{12}独立地为 H 或 (C_1-C_6) 烷基，任选地被 4 至 8 元杂环烷基环取代；并且

[0021] m 和 n 均独立地是 1、2、3 或 4。

[0022] 在某些实施方式中，式 (I) 的化合物是 Y 为 -$(CH_2)_3$-NR_9R_{10}的化合物。

[0023] 在具体实施方式中，式 (I) 的化合物是 R_1为具有独立地选自由 N、O、和 S 组成的组中的 1-3 个杂原子的芳香族 5 元杂环或 6 元杂环的化合物。

[0024] 在具体实施方式中，式 (I) 的化合物是 R_1为吡啶基或嘧啶基的化合物。

[0025] 在具体实施方式中，式 (I) 的化合物是 R_1为具有 1 或 2 个氮原子并且任选地具有 1 或 2 个硫原子的芳香族 5 元杂环的化合物。在具体实施方式中，式 (I) 的化合物是 R_1为噻唑基、异噻唑基、或噻二唑基的化合物。在具体实施方式中，式 (I) 的化合物是 R_1为噻唑基的化合物。在具体实施方式中，式 (I) 的化合物是 R_1为 1,2,4- 噻二唑 -5- 基的化合物。

[0026] 在具体实施方式中，式 (I) 的化合物是 R_2在每次出现时独立地为 -F 或 -Cl 的化合物。

[0027] 在具体实施方式中，式 (I) 的化合物是 n 为 1、2 或 3 的化合物。在具体实施方式中，式 (I) 的化合物是 n 为 2 的化合物。

[0028] 在具体实施方式中，式 (I) 的化合物是 Z 为 -O- 的化合物。

[0029] 在具体实施方式中，式 (I) 的化合物是 R_3在每次出现时独立地为 -H、-F、-Cl、或 -Br 的化合物。在具体实施方式中，式 (I) 的化合物是 R_3为 -H 或 -Cl 的化合物。在具体实施方式中，式 (I) 的化合物是 R_3为 -Cl 的化合物。

[0030] 在具体实施方式中，式 (I) 的化合物是 m 为 1、2、或 3 的化合物。在具体实施方式中，式 (I) 的化合物是 m 为 1 的化合物。

[0031] 在具体实施方式中，式 (I) 的化合物是 R_9为 (C_1-C_6) 烷基的化合物；其中，R_9任选地进一步被选自由 -COOH、-COOMe、-$CONH_2$、和 NH_2组成的组中的 1 或 2 个取代基取代。在具体实施方式中，式 (I) 的化合物是 R_9是甲基或乙基的化合物。在具体实施方式中，式 (I) 的化合物是 R_9进一步被 -COOH 取代的化合物。

[0032] 在具体实施方式中，式 (I) 的化合物是 R_{10}为 -H、-COMe、-COOEt 的化合物。在具体实施方式中，式 (I) 的化合物是 R_{10}为 -H 或 -COMe 的化合物。在具体实施方式中，式 (I) 的化合物是 R_{10}为 -H 的化合物。

[0033] 在具体实施方式中，式 (I) 的化合物是 R_9和 R_{10}一起形成 4 至 8 元杂环烷基环，其中，所述杂环烷基环被选自由 -COOH、-COOMe、-COOEt、CH_2-COOH 和 -NH_2组成的组中的 1 或 2 个基团取代。在具体实施方式中，式 (I) 的化合物是 R_9和 R_{10}一起形成 4 至 8 元杂环烷基环的化合物，其中，所述杂环烷基环被选自由 -COOH、CH_2-COOH 和 -NH_2组成的组中的 1 或 2 个基团取代。

[0034] 在具体实施方式中，式 (I) 的化合物是 R_9和 R_{10}一起形成被选自由 -COOH、-COOMe、-COOEt、-CH_2-COOH、-CH_2-COOMe、-CH_2-COOEt 和 -NH_2组成的组中的 1 或 2 个基团取代的哌啶的化合物。在具体实施方式中，式 (I) 的化合物是 R_9和 R_{10}一起形成被选自由 -COOH、-CH_2-COOH 和 -NH_2组成的组中的 1 或 2 个基团取代的哌啶的化合物。

[0035] 在某些实施方式中，式 (I) 的化合物是 Y 为 -X-C(= O)NR_4R_5的化合物。

[0036] 在具体实施方式中，式 (I) 的化合物是 R_1为具有独立地选自由 N、O、和 S 组成的组中的 1-3 个杂原子的芳香族 5 元杂环或 6 元杂环的化合物。

[0037] 在具体实施方式中，式 (I) 的化合物是 R_1为吡啶基或嘧啶基的化合物。

[0038] 在具体实施方式中，式 (I) 的化合物是 R_1为具有 1 或 2 个氮原子并且任选地具有 1 或 2 个硫原子的芳香族 5 元杂环的化合物。在具体实施方式中，式 (I) 的化合物是 R_1为噻唑基、异噻唑基、或噻二唑基的化合物。在具体实施方式中，式 (I) 的化合物是 R_1为噻唑基的化合物。在具体实施方式中，式 (I) 的化合物是 R_1为 1,2,4- 噻二唑 -5- 基的化合物。

[0039] 在具体实施方式中，式 (I) 的化合物是 R_2在每次出现时独立地为 -F 或 -Cl 的化合物。

[0040] 在具体实施方式中，式 (I) 的化合物是 n 为 1、2 或 3 的化合物。在具体实施方式中，式 (I) 的化合物是 n 为 2 的化合物。

[0041] 在具体实施方式中，式 (I) 的化合物是 Z 为 -O- 的化合物。

[0042] 在具体实施方式中，式 (I) 的化合物是 R_3在每次出现时独立地为 -F、-Cl、或 -Br 的化合物。在具体实施方式中，式 (I) 的化合物是 R_3为 -H 或 -Cl 的化合物。在具体实施方式中，式 (I) 的化合物是 R_3为 -Cl 的化合物。

[0043] 在具体实施方式中，式 (I) 的化合物是 m 为 1、2、或 3 的化合物。在具体实施方式

中，式（I）的化合物是 m 为 1 的化合物。

[0044] 在具体实施方式中，式（I）的化合物是 X 为 5 元杂芳基或 6 元杂芳基的化合物。在具体实施方式中，式（I）的化合物是 X 为吡啶基或嘧啶基的化合物。在具体实施方式中，式（I）的化合物是 X 为吡啶基的化合物。

[0045] 在具体实施方式中，式（I）的化合物是 R_4为 H 和 R_5为（C_1-C_9）烷基的化合物。

[0046] 在具体实施方式中，式（I）的化合物是 R_5为被选自由 $-CO_2H$、$-CO_2R_6$、和 $-CONR_7R_8$组成的组中的 1 或 2 个取代基取代的甲基或乙基的化合物。

[0047] 在具体实施方式中，式（I）的化合物是 R_6为（C_1-C_6）烷基的化合物。

[0048] 在具体实施方式中，式（I）的化合物是 R_5是由 $-CO_2H$ 取代的甲基或乙基的化合物。

[0049] 在某些实施方式中，式（I）的化合物是 Y 为 4,5,6,7- 四氢吡唑并［1,5-α］嘧啶 -（2- 基或 3- 基）的化合物。在具体实施方式中，式（I）的化合物是 Y 为 4,5,6,7- 四氢吡唑并［1,5-α］嘧啶 -3- 基）的化合物。

[0050] 在具体实施方式中，式（I）的化合物是 R_1为具有独立地选自由 N、O、和 S 组成的组中的 1-3 个杂原子的芳香族 5 元杂环或 6 元杂环的化合物。

[0051] 在具体实施方式中，式（I）的化合物是 R_1为吡啶基或嘧啶基的化合物。

[0052] 在具体实施方式中，式（I）的化合物是 R_1为具有 1 或 2 个氮原子并且任选地具有 1 或 2 个硫原子的芳香族 5 元杂环的化合物。在具体实施方式中，式（I）的化合物是 R_1为噻唑基、异噻唑基、或噻二唑基的化合物。在具体实施方式中，式（I）的化合物是 R_1为噻唑基的化合物。在具体实施方式中，式（I）的化合物是 R_1为 1,2,4- 噻二唑 -5- 基的化合物。

[0053] 在具体实施方式中，式（I）的化合物是 R_2在每次出现时独立地为 -F 或 -Cl 的化合物。

[0054] 在具体实施方式中，式（I）的化合物是 n 为 1、2 或 3 的化合物。在具体实施方式中，式（I）的化合物是 n 为 2 的化合物。

[0055] 在具体实施方式中，式（I）的化合物是 Z 为 -O- 的化合物。

[0056] 在具体实施方式中，式（I）的化合物是 R_3在每次出时独立地为 -F、-Cl、或 -Br 的化合物。在具体实施方式中，式（I）的化合物是 R_3为 -H 或 -Cl 的化合物。在具体实施方式中，式（I）的化合物是 R_3为 -Cl 的化合物。

[0057] 在具体实施方式中，式（I）的化合物是 m 为 1、2、或 3 的化合物。在具体实施方式中，式（I）的化合物是 m 为 1 的化合物。

[0058] 在某些实施方式中，式（I）的化合物是以下化合物：

[0059] 3-（4-（2-（4-（N-（1,2,4- 噻二唑 -5- 基）氨磺酰基）-2- 氯 -5- 氟苯氧基）-5- 氯苯基）吡啶酰胺基）丙酸、

[0060] 2-（4-（2-（4-（N-（1,2,4- 噻二唑 -5- 基）氨磺酰基）-2- 氯 -5- 氟苯氧基）-5- 氯苯基）吡啶酰胺基）乙酸、

[0061] 5-（4-（2-（4-（N-（1,2,4- 噻二唑 -5- 基）氨磺酰基）-2- 氯 -5- 氟苯氧基）-5- 氯苯基）吡啶酰胺基）戊酸、

[0062] 4-（4-（2-（4-（N-（1,2,4- 噻二唑 -5- 基）氨磺酰基）-2- 氯 -5- 氟苯氧基）-5- 氯苯基）吡啶酰胺基）丁酸、

[0063] 2-（4-（2-（4-（N-（1,2,4- 噻二唑 -5- 基）氨磺酰基）-2- 氯 -5- 氟苯氧基）-5- 氯

苯基）吡啶酰胺基）丙酸、

[0064] (R)-2-(4-(2-(4-(N-(1,2,4-噻二唑-5-基）氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基）吡啶酰胺基）丙酸、

[0065] 2-(6-(2-(4-(N-(1,2,4-噻二唑-5-基）氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基）吡啶酰胺基）乙酸、

[0066] (S)-2-(4-(2-(4-(N-(1,2,4-噻二唑-5-基）氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基）吡啶酰胺基）丙酸、

[0067] 3-(4-(2-(4-(N-(1,2,4-噻二唑-5-基）氨磺酰基)-2-氰基苯氧基)-5-氯苯基）吡啶酰胺基）丙酸、

[0068] 3-(4-(2-(4-(N-(1,2,4-噻二唑-5-基）氨磺酰基)-2,5-二氟苯氧基)-5-氯苯基）吡啶酰胺基）丙酸、

[0069] 2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）氨基）乙酸、

[0070] 3-((3-(2-(4-(N-(1,2,4-噻二唑-5-基）氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基）丙基）氨基）丙酸、

[0071] 2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-2-基）氨磺酰基）苯氧基）苯基）丙基）氨基）乙酸、

[0072] 1-(3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）哌啶)-4-羧酸、

[0073] 3-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）氨基）丙酸、

[0074] 4-氨基-1-(3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）哌啶)-4-羧酸、

[0075] 2-氨基-4-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）氨基）丁酸、

[0076] 2-((3-(5-氯-2-(2,5-二氟-4-(N-(噻唑-2-基）氨磺酰基）苯氧基）苯基）丙基）氨基）乙酸、

[0077] 1-(3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）哌啶)-3-羧酸、

[0078] 2-((3-(2-(4-(N-(1,2,4-噻二唑-5-基）氨磺酰基)-2-氯-5-氟苯氧基）苯基）丙基）氨基）乙酸、

[0079] 2-((3-(5-氯-2-(2,5-二氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）氨基）乙酸、

[0080] 3-((3-(5-氯-2-(2,5-二氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）氨基）丙酸、

[0081] 3-((3-(5-氯-2-(2-氰基-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）氨基）丙酸、

[0082] 甲基2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）氨基）乙酸酯、

[0083] 3-((3-(2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)-5-氟苯基)丙基)氨基)丙酸、

[0084] 3-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)丙酰胺、

[0085] 2-(N-(3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)乙酰氨基)乙酸、

[0086] 2-(1-(3-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)丙基)哌啶-4-基)乙酸、

[0087] 3-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-2-基)氨磺酰基)苯氧基)苯基)丙基)氨基)丙酸、

[0088] 2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)-N-甲基乙酰胺、

[0089] 5-氯-4-(4-氯-2-(3-((2-(甲磺酰基)乙基)氨基)丙基)苯氧基)-2-氟-N-(噻唑-4-基)苯磺酰胺、

[0090] 1-(3-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)丙基)哌啶-4-羧酸;或

[0091] 5-氯-4-(4-氯-2-(4,5,6,7-四氢吡唑并[1,5-α]嘧啶-3-基)-2-氟-N-(噻唑-4-基)苯磺酰胺;或可药用的盐、或其立体异构形式或互变异构形式。

[0092] 在具体实施方式中,式(I)的化合物是以下化合物:

[0093] 2-(4-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)吡啶酰胺基)乙酸、

[0094] 3-(4-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)吡啶酰胺基)丙酸、

[0095] 2-(4-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)吡啶酰胺基)丙酸、或

[0096] 3-((3-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)丙基)氨基)丙酸;或可药用的盐,或其立体异构形式或互变异构形式。

[0097] 本文提供了用于治疗神经性疼痛的方法,所述方法包括将治疗有效量的式(I)的化合物或治疗有效量的该化合物的盐或其溶剂化物或互变异构形式给药于有此需要的受试者。

[0098] 本文提供了用于治疗疼痛的方法,所述方法包括使用式(I)的化合物作为电压依赖性钠通道抑制剂。在具体实施方式中,这些方法是其中的疼痛为神经性疼痛、伤害性疼痛或炎性疼痛的方法。在具体实施方式中,这些方法是其中的电压依赖性钠通道为NaV1.7的方法。

[0099] 本文提供了药物组合物,该药物组合物包括式(I)的化合物和可药用的载体。在具体实施方式中,药物组合物是所述组合物适用于局部给药、口服给药、皮下注射给药或静脉给药的药物组合物。

[0100] 本文提供了用于预防或治疗受试者中的疼痛的方法,其中所述方法包括将治疗有效量的式(I)的化合物给药于需要这种预防或治疗的受试者。在具体实施方式中,所述

方法是其中的治疗有效量对减轻受试者中的疼痛有效的方法，其中式（I）的所述化合物以 0.1mg/kg 至 1,000mg/kg 的剂量、以 0.5mg/kg 至 100mg/kg 的剂量、以 1mg/kg 至 50mg/kg 的剂量或以 5mg/kg 的剂量在福尔马林试验（在阶段 1 或阶段 2，或两个阶段中）（参见 5.1.2 小节）表现出减小疼痛反应。在某些实施方式中，本文提供的式（I）的化合物表现出在福尔马林试验（在阶段 1 或阶段 2，或两个阶段中）中比空白对照减少至少 10％、20％、30％、40％、50％、60％、70％、80％、90％、95％、98％、99％、或 100％，或在任意的列举的百分比范围之间（例如，10-20％、10-30％、10-40％、20-30％、或 20-40％）的范围内的疼痛反应。在具体实施方式中，所述方法是是疼痛为以下各项的方法：伤害性疼痛，如由物理创伤导致的疼痛（例如，皮肤的切口或挫伤；或化学烧伤或热烧伤）、骨关节炎、类风湿性关节炎或肌腱炎；肌筋膜疼痛；神经性疼痛，如与中风、糖尿病性神经病、梅毒性神经病、带状疱疹后神经痛、三叉神经痛、纤维肌痛、或由药物医源性地诱导的疼痛性神经病相关的神经性疼痛；或混合型疼痛（即，具有伤害性和神经性成分的疼痛）；内脏疼痛；头痛（例如，偏头痛）；CRPS；CRPS Ⅰ型；CRPS Ⅱ型；RSD；反射性神经血管营养不良；反射性营养不良；交感神经维持疼痛综合征；灼痛；祖德克骨萎缩；痛觉神经营养不良；肩手综合征；创伤后营养不良；自主机能障碍；自身免疫相关的疼痛；炎症相关的疼痛；癌症相关的疼痛；幻肢痛；慢性疲劳综合征；手术后的疼痛；脊髓损伤性疼痛；卒中后中枢痛；神经根病；对皮肤的温度、轻触或颜色变化的敏感性（痛觉超敏）；源于高热或低热病症的疼痛；和其它疼痛病症（例如，糖尿病性神经病、梅毒性神经病、带状疱疹后神经痛、三叉神经痛）；慢性疼痛；或急性疼痛。

[0101] 本文提供了调控电压依赖性钠通道的活性的方法，其中所述方法包括使表达电压依赖性钠通道的细胞与式（I）的化合物接触。在具体实施方式中，所述方法是其中的电压依赖性钠通道为 NaV1.7 的方法。在具体实施方式中，所述方法是导致抑制电压依赖性钠通道的方法。

具体实施方式

[0102] 4.1 定义

[0103] 如本文所用“化合物（compound）”或“多种化合物（compounds）”包含式（I）的化合物、式（Ia）的化合物、式（Ib）的化合物、式（Ic）的化合物、式（Id）的化合物、列于表 1 的化合物、或列于表 2 的化合物。

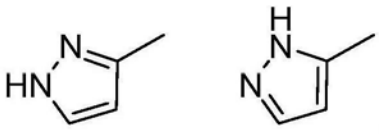
[0104] “一种或多种可药用的盐”是指从包含无机酸或碱和有机酸或碱的可药用的无毒的酸或碱制备的盐。化合物抑制剂的合适的可药用的碱加成盐包括，但不限于由铝、钙、锂、镁、钾、钠和锌制成的金属盐；或由赖氨酸、N,N'-二苄基乙二胺、氯普鲁卡因、胆碱、二乙醇胺、乙二胺、葡甲胺（N-甲基葡糖胺）和普鲁卡因制成的有机盐。合适的无毒的酸包括，但不限于无机酸和有机酸，如乙酸、海藻酸、邻氨基苯甲酸、苯磺酸、苯甲酸、樟脑磺酸、柠檬酸、乙烯磺酸、甲酸、反丁烯二酸、糠酸、半乳糖醛酸、葡萄糖酸、葡糖醛酸、谷氨酸、乙醇酸、氢溴酸、盐酸、羟乙磺酸、乳酸、顺丁烯二酸、苹果酸、扁桃酸、甲磺酸、粘酸、硝酸、双羟萘酸、泛酸、苯乙酸、磷酸、丙酸、水杨酸、硬脂酸、琥珀酸、对氨基苯磺酸、硫酸、酒石酸、和对甲苯磺酸。具体的无毒的酸包括盐酸、氢溴酸、磷酸、硫酸和甲磺酸。本领域熟知的其他无毒的酸参见例如，雷明顿药学，第 18 版，Mack 出版社出版，宾夕法尼亚州伊斯顿（1990

年)(Remington's Pharmaceutical Sciences,18th eds.,Mack Publishing,Easton PA(1990)) 或者雷明顿 :药学的科学与实践,第 19 版,Mack 出版社出版,宾夕法尼亚州伊斯顿 (1995 年)(Remington :The Science and Practice of Pharmacy,19th eds.,Mack Publishing,Easton PA(1995))。

[0105] "立体异构体"或"立体异构形式"是指化合物的一种立体异构体,该化合物基本上不含有其他立体异构体。例如,具有一个手性中心的立体异构纯化合物基本上不含有该化合物的反向对映异构体。具有两个手性中心的立体异构纯化合物基本上不含有该化合物的其他非对映异构体。典型的立体异构纯化合物包含大于约 80 重量%该化合物的一种立体异构体并且小于约 20 重量%该化合物的其他立体异构体,大于约 90 重量%该化合物的一种立体异构体并且小于约 10 重量%该化合物的其他立体异构体,大于约 95 重量%该化合物的一种立体异构体并且小于约 5 重量%该化合物的其他立体异构体,或大于约 97 重量%该化合物的一种立体异构体并且小于约 3 重量%该化合物的其他立体异构体。化合物可以有手性中心并且可以以外消旋体、单个对映异构体或非对映异构体、以及它们的混合物出现。所有这些异构形式包括在本文所公开的实施方式中,包括它们的混合物。使用这些化合物的立体异构体纯形式以及使用这些形式的混合物都包括在本文所公开的实施方式中。例如,本文所公开的方法和组合物中可以使用包含具体的化合物的等量的或非等量的对映异构体。可以使用标准技术,如手性柱或手性拆分剂不对称地合成或拆分这些异构体。参见,例如, Jacques,J. 等,对映异构体、外消旋体和拆分 (威利跨学科科学出版社,纽约,1981 年)(Jacques,J.et al.,Enantiomers,Racemates and Resolutions(Wiley Interscience,New York,1981)) ;Wilen,S.H. 等, 四面体,33:2725(1977 年)(Wilen,S.H.,et al.,Tetrahedron 33:2725(1977)) ;Eliel,E.L., 碳化合物的立体化学,麦格劳希尔,纽约,1962 年 (Eliel,E.L.,Stereochemistry of Carbon Compounds(McGraw Hill,NY,1962)) ;以及 Wilen,S.H., 拆分剂和光分辨率的列表,第 268 页 (E.L.Eliel,Ed., 圣母玛利亚大学 ,Notre Dame,IN,1972 年)(Wilen,S.H.,Tables of Resolving Agents and Optical Resolutions p.268(E.L.Eliel,Ed.,Univ.of Notre Dame Press,Notre Dame,IN,1972))。

[0106] "互变异构体"是指彼此处于平衡的化合物的异构形式。异构形式的浓度将取决于化合物所在的环境并且可以根据例如该化合物是固体还是有机溶液或水溶液而不同。例如,在水溶液中,吡唑可以出现以下异构形式,其被称为彼此的互变异构体 :

[0107]



[0108] 本领域的技术人员容易理解的是,多种多样的官能团和其他结构可以出现互变异构并且本文提供的化合物的所有互变异构体都在本文所公开的范围内。

[0109] "芳基"基团是有 6-14 个碳原子的具有单环 (例如,苯基) 或多个稠环 (例如,萘基或蒽基) 的芳香族碳环基团。在一些实施方式中,芳基基团在该基团的环部分中包含 6-14 个碳原子,并且其他的芳基基团中包含 6-12 或甚至 6-10 个碳原子。具体的芳基包括,但不限于苯基、萘基等等。

[0110] “杂芳基”基团是在杂芳香环体系中具有 1-4 个杂原子作为环原子的芳基环体系，其中，剩余的原子是碳原子。在一些实施方式中，杂芳基基团在该基团的环部分中包含 5-6 个碳原子，并且其他的杂芳基基团中包含 6-9 或甚至 6-10 个原子。合适的杂原子包括氧、硫和氮。在某些实施方式中，杂芳环体系是单环或双环。实例包括，但不限于诸如如下的基团：吡咯基、吡唑基、咪唑基、三唑基、四唑基、恶唑基、异恶唑基、噻唑基、异噻唑基、噻二唑基（例如，1,2,4- 噻二唑基）、吡咯基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯硫基、苯并噻吩基、呋喃基、苯并呋喃基、吲哚基、氮杂吲哚基（例如，吡咯并吡啶或 1H- 吡咯并 [2,3-b] 吡啶基）、吲唑基、苯并咪唑基（例如，1H- 苯并 [d] 咪唑基）、咪唑并吡啶基、吡唑并吡啶、三唑并吡啶基、苯并三唑基、苯并恶唑基、苯并噻唑基、苯并噻二唑基、异恶唑吡啶、硫萘基、嘌呤基、黄嘌呤基、腺嘌呤基、鸟嘌呤基、喹啉基、异喹啉基、四氢喹啉基、喹恶啉基、和喹唑啉基团。

[0111] “部分未饱的和或芳香族的杂环”是在杂芳香环体系中具有 1-4 个杂原子作为环原子的部分未饱和的或芳香族的环体系，其中，剩余的原子是碳原子。如果“部分未饱和的或芳香族的杂环”是芳香杂环，则芳香杂环是如上定义的“杂芳基”。在一个实施方式中，部分未饱和的或芳香族的杂环是部分未饱和是或芳香族的 5 元杂环或 6 元杂环。部分未饱和的杂环的实例包括，但不限于诸如如下的基团：2,5- 二氢 -1H- 吡咯基、2,5- 二氢呋喃基、2,5- 二氢噻吩基、4,5- 二氢恶唑基、4,5- 二氢噻唑基、4,5- 二氢 -1H- 咪唑基、4,5- 二氢 -1H-1,2,3- 三唑基，1,2,5,6- 四氢吡啶基、和 1,4,5,6- 四氢嘧啶基团。

[0112] “杂环烷基”基团是非芳香族环烷基，其中 1-4 个环碳原子由 O、S、N 组成的组的杂原子独立取代。杂环烷基基团的实例包括，但不限于吗啉基、吡咯烷基、吡嗪基、(1,4)- 二氧己环基和 (1,3)- 二氧戊环基。杂环烷基也可以结合在任意的环原子上（即，在任意的碳原子或杂环的杂原子上）。在一个实施方式中，杂环烷基是 5 元杂环烷基或 6 元杂环烷基。

[0113] “烷基”基团是饱和的直链或支链非环状烃，其具有例如 1-12 个碳原子、1-9 个碳原子、1-6 个碳原子、1-4 个碳原子或 2-6 个碳原子。典型的烷基基团包括 - 甲基、- 乙基、- 正丙基、- 正丁基、- 正戊基和 - 正己基；而支链烷基包括 - 异丙基、- 仲丁基、- 异丁基、- 叔丁基、- 异戊基、2- 甲基戊基、3- 甲基戊基、4- 甲基戊基、2,3- 二甲基丁基等等。

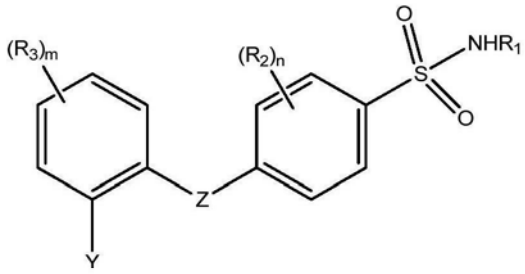
[0114] “环烷基”基团是具有单环或多个稠合环或桥环的 3-12 个碳原子的饱和环状烷基基团。在一些实施方式中，环烷基基团指的是具有 4-12 个环成员，而在其他实施方式中，环碳原子的数量在例如 3 至 5，或 3 至 6，或 3 至 7 的范围内。这些环烷基团包括，例如，环丙基、环丁基、环戊基、环己基、环庚基、环辛基等的单环结构，或如金刚烷基等的多环或桥环结构。

[0115] “有此需要的受试者”指的是需要用本文提供的任何方法治疗的哺乳动物（例如，人、狗、马、或猫）。

[0116] 4.2 化合物

[0117] 本文提供了式 (I) 的化合物，

[0118]



式（I）

[0119] 或可药用的盐，或其立体异构形式或互变异构形式，其中：

[0120] Z 是 -O- 或 -S-；

[0121] Y 是 -X-C(= O)NR_4R_5、-$(CH_2)_3$-NR_9R_{10}、或 4,5,6,7- 四氢吡唑并 [1,5-α] 嘧啶 -(2- 基或 3- 基）；

[0122] X 是 (C_6-C_{10}) 芳基或 5 元杂芳基或 6 元杂芳基；

[0123] R_1是部分未饱和的或芳香族的 5 元杂环或 6 元杂环；

[0124] R_2在每次出时独立地为 -F、-Cl、-Br、-CH_3或 -CN；

[0125] R_3在每次出时独立地为 -H、-F、-Cl、-Br、-CF_3、-OCF_3、-CN、(C_1-C_{12}) 烷基、或 (C_1-C_{12}) 烷氧基；

[0126] R_4和 R_5均独立地是 H、(C_1-C_9) 烷基、(C_4-C_{12}) 环烷基或 R_4和 R_5一起形成 5 元杂环烷基环至 7 元杂环烷基环；前提条件是：

[0127] R_4和 R_5都不是 H；并且

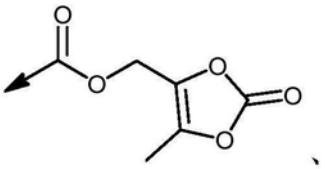
[0128] R_4和 R_5中至少一个独立地被或 R_4和 R_5一起形成的所述杂环烷基环被选自由 -CO_2H、-CO_2R_6、-CN、-OH、-$CONR_7R_8$和 -NR_7R_8组成的组中的 1 或 2 个取代基取代；其中：

[0129] R_6是 (C_1-C_{12}) 烷基；

[0130] R_7和 R_8各自独立地是 H、(C_1-C_{12}) 烷基，或 R_7和 R_8一起形成 4 元杂环烷基环至 7 元杂环烷基环；

[0131] R_9是 (C_1-C_6) 烷基、(C_3-C_8) 环烷基、吡唑基或吡啶基；其中，R_9任选地进一步被选自由 -COOH、-$COOR_{11}$、-$CONR_{11}R_{12}$、-SO_2R_{11}、-$SO_2NR_{11}R_{12}$、-OH、-CN、-OR_{11}、和 -$NR_{11}R_{12}$组成的组中的 1 或 2 个取代基取代；其中，R_{11}和 R_{12}可以形成 6 元杂环烷基环；

[0132] R_{10}是 R_{11}、-COR_{11}、-$COOR_{11}$、-SO_2R_{11}、5- 甲基 -2- 氧代 -1,3- 二氧杂环戊烯 -4- 基、



-COO-$CH(CH_3)OCOCH(CH_3)_2$；或 R_9和 R_{10}一起形成哌嗪酮或 4 元杂环烷基环至 8 元杂环烷基环，其中所述杂环烷基环被选自由 -COOH、-$COOR_{11}$、-CH_2-$COOR_{11}$、-OH、-NH_2、-CN、和 (C_1-C_8) 烷氧基组成的组中的 1 或 2 个取代基取代；

[0133] R_{11}和 R_{12}独立地是 H 或 (C_1-C_6) 烷基，任选地被 4 元杂环烷基环至 8 元杂环烷基环取代；并且

[0134] m 和 n 均独立地是 1、2、3 或 4。

[0135] 在某些实施方式中，式 (I) 的化合物是 Y 为 -$(CH_2)_3$-NR_9R_{10}的化合物。

[0136] 在具体实施方式中，式 (I) 的化合物是 R_1是芳香族 5 元杂环或 6 元杂环的化合物，其具有独立地选自由 N、O、和 S 组成的组中的 1-3 个杂原子。

[0137] 在具体实施方式中，式 (I) 的化合物是 R_1为吡啶基或嘧啶基的化合物。

[0138] 在具体实施方式中，式 (I) 的化合物是 R_1是芳香族 5 元杂环的化合物，其具有 1 或 2 个氮原子并且任选地具有 1 或 2 个硫原子。在具体实施方式中，式 (I) 的化合物是 R_1为噻唑基、异噻唑基、或噻二唑基的化合物。在具体实施方式中，式 (I) 的化合物是 R_1为噻唑基的化合物。在具体实施方式中，式 (I) 的化合物是 R_1为 1,2,4- 噻二唑 -5- 基的化合物。

[0139] 在具体实施方式中，式 (I) 的化合物是 R_2在每次出时独立地为 -F 或 -Cl 的化合物。

[0140] 在具体实施方式中，式 (I) 的化合物是 n 为 1、2 或 3 的化合物。在具体实施方式中，式 (I) 的化合物是 n 为 2 的化合物。

[0141] 在具体实施方式中，式 (I) 的化合物是 Z 为 -O- 的化合物。

[0142] 在具体实施方式中，式 (I) 的化合物是 R_3在每次出时独立地为 -H、-F、-Cl、或 -Br 的化合物。在具体实施方式中，式 (I) 的化合物是 R_3为 -H 或 -Cl 的化合物。在具体实施方式中，式 (I) 的化合物是 R_3为 -Cl 的化合物。

[0143] 在具体实施方式中，式 (I) 的化合物是 m 为 1、2、或 3 的化合物。在具体实施方式中，式 (I) 的化合物是 m 为 1 的化合物。

[0144] 在具体实施方式中，式 (I) 的化合物是 R_9为 (C_1-C_6) 烷基的化合物；其中，R_9任选地进一步被选自由 -COOH、-COOMe、-$CONH_2$、和 NH_2组成的组的 1 或 2 个取代基取代。在具体实施方式中，式 (I) 的化合物是 R_9是甲基或乙基的化合物。在具体实施方式中，式 (I) 的化合物是 R_9进一步被 -COOH 取代的化合物。

[0145] 在具体实施方式中，式 (I) 的化合物是 R_{10}为 -H、-COMe、-COOEt 的化合物。在具体实施方式中，式 (I) 的化合物是 R_{10}为 -H 或 -COMe 的化合物。在具体实施方式中，式 (I) 的化合物是 R_{10}为 -H 的化合物。

[0146] 在具体实施方式中，式 (I) 的化合物是 R_9和 R_{10}一起形成 4 至 8 元杂环烷基环，其中，所述杂环烷基环被选自由 -COOH、-COOMe、-COOEt、CH_2-COOH、和 -NH_2组成的组的 1 或 2 个基团取代。在具体实施方式中，式 (I) 的化合物是 R_9和 R_{10}一起形成 4 至 8 元杂环烷基环的化合物，其中，所述杂环烷基环由选自由 -COOH、CH_2-COOH、和 -NH_2组成的组的 1 或 2 个基团取代。

[0147] 在具体实施方式中，式 (I) 的化合物是 R_9和 R_{10}一起形成由选自由 -COOH、-COOMe、-COOEt、CH_2-COOH、-CH_2-COOMe、-CH_2-COOEt 和 -NH_2组成的组的 1 或 2 个基团取代的哌啶的化合物。在具体实施方式中，式 (I) 的化合物是 R_9和 R_{10}一起形成被选自由 -COOH、CH_2-COOH、和 -NH_2组成的组的 1 或 2 个基团取代的哌啶的化合物。

[0148] 在某些实施方式中，式 (I) 的化合物是 Y 为 -X-C(= O)NR_4R_5的化合物。

[0149] 在具体实施方式中，式 (I) 的化合物是 R_1是芳香 5 元杂环或 6 元杂环的化合物，其具有独立地选自由 N、O、和 S 组成的组的 1-3 个杂原子。

[0150] 在具体实施方式中，式 (I) 的化合物是 R_1为吡啶基或嘧啶基的化合物。

[0151] 在具体实施方式中，式 (I) 的化合物是 R_1是芳香族 5 元杂环的化合物，其具有 1 或 2 个氮原子和任选地具有 1 或 2 个硫原子。在具体实施方式中，式 (I) 的化合物是 R_1为噻

唑基、异噻唑基、或噻二唑基的化合物。在具体实施方式中，式 (I) 的化合物是 R_1为噻唑基的化合物。在具体实施方式中，式 (I) 的化合物是 R_1为 1,2,4- 噻二唑 -5- 基的化合物。

[0152] 在具体实施方式中，式 (I) 的化合物是 R_2在每次出时独立地为 -F 或 -Cl 的化合物。

[0153] 在具体实施方式中，式 (I) 的化合物是 n 为 1、2、或 3 的化合物。在具体实施方式中，式 (I) 的化合物是 n 为 2 的化合物。

[0154] 在具体实施方式中，式 (I) 的化合物是 Z 为 -O- 的化合物。

[0155] 在具体实施方式中，式 (I) 的化合物是 R_3在每次出时独立地为 -F、-Cl、或 -Br 的化合物。在具体实施方式中，式 (I) 的化合物是 R_3为 -H 或 -Cl 的化合物。在具体实施方式中，式 (I) 的化合物是 R_3为 -Cl 的化合物。

[0156] 在具体实施方式中，式 (I) 的化合物是 m 为 1、2、或 3 的化合物。在具体实施方式中，式 (I) 的化合物是 m 为 1 的化合物。

[0157] 在具体实施方式中，式 (I) 的化合物是 X 为 5 元杂芳基或 6 元杂芳基的化合物。在具体实施方式中，式 (I) 的化合物是 X 为吡啶基或嘧啶基的化合物。在具体实施方式中，式 (I) 的化合物是 X 为吡啶基的化合物。

[0158] 在具体实施方式中，式 (I) 的化合物是 R_4为 H 和 R_5为 (C_1-C_9) 烷基的化合物。

[0159] 在具体实施方式中，式 (I) 的化合物是 R_5是由选自由 $-CO_2H$、$-CO_2R_6$、和 $-CONR_7R_8$组成的组的 1 或 2 个取代基取代的甲基或乙基的化合物。

[0160] 在具体实施方式中，式 (I) 的化合物是 R_6为 (C_1-C_6) 烷基的化合物。

[0161] 在具体实施方式中，式 (I) 的化合物是 R_5是由 $-CO_2H$ 取代的甲基或乙基的化合物。

[0162] 在某些实施方式中，式 (I) 的化合物是 Y 为 4,5,6,7- 四氢吡唑并 [1,5-α] 嘧啶 -(2- 基或 3- 基) 的化合物。在具体实施方式中，式 (I) 的化合物是 Y 为 4,5,6,7- 四氢吡唑并 [1,5-α] 嘧啶 -3- 基) 的化合物。

[0163] 在具体实施方式中，式 (I) 的化合物是 R_1是芳香族 5 元杂环或 6 元杂环的化合物，其具有独立地选自由 N、O、和 S 组成的组的 1-3 个杂原子。

[0164] 在具体实施方式中，式 (I) 的化合物是 R_1为吡啶基或嘧啶基的化合物。

[0165] 在具体实施方式中，式 (I) 的化合物是 R_1为具有 1 或 2 个氮原子且任选地具有 1 或 2 个硫原子的芳香族 5 元杂环的化合物。在具体实施方式中，式 (I) 的化合物是 R_1为噻唑基、异噻唑基、或噻二唑基的化合物。在具体实施方式中，式 (I) 的化合物是 R_1为噻唑基的化合物。在具体实施方式中，式 (I) 的化合物是 R_1为 1,2,4- 噻二唑 -5- 基的化合物。

[0166] 在具体实施方式中，式 (I) 的化合物是 R_2在每次出时独立地为 -F 或 -Cl 的化合物。

[0167] 在具体实施方式中，式 (I) 的化合物是 n 为 1、2、或 3 的化合物。在具体实施方式中，式 (I) 的化合物是 n 为 2 的化合物。

[0168] 在具体实施方式中，式 (I) 的化合物是 Z 为 -O- 的化合物。

[0169] 在具体实施方式中，式 (I) 的化合物是 R_3在每次出时独立地为 -F、-Cl、或 -Br 的化合物。在具体实施方式中，式 (I) 的化合物是 R_3为 -H 或 -Cl 的化合物。在具体实施方式中，式 (I) 的化合物是 R_3为 -Cl 的化合物。

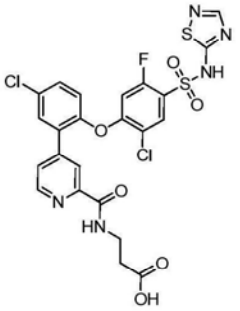
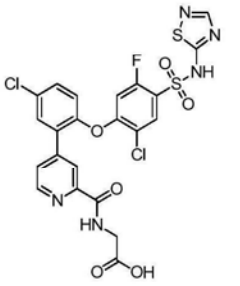
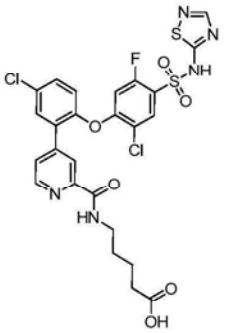
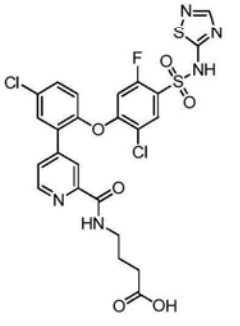
[0170] 在具体实施方式中，式 (I) 的化合物是 m 为 1、2、或 3 的化合物。在具体实施方式

中，式（I）的化合物是 m 为 1 的化合物。

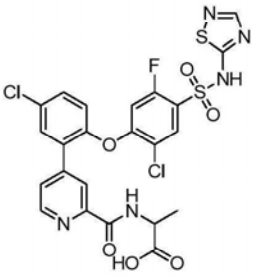
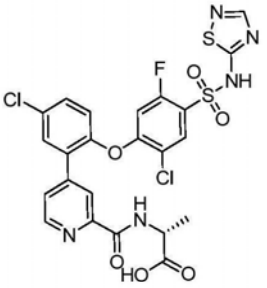
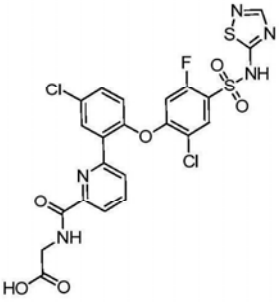
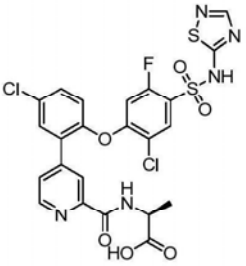
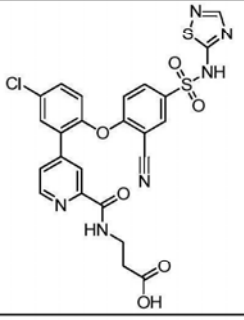
[0171] 在某些实施方式中，式（I）的化合物是选自由表 1 中的化合物或可药用的盐、或其立体异构或互变异构形式组成的组的化合物。

[0172] 表 1

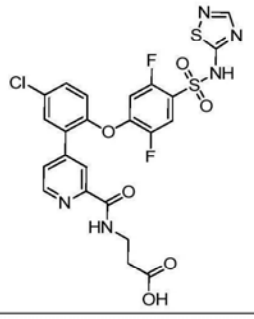
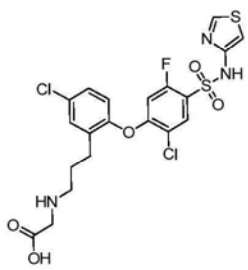
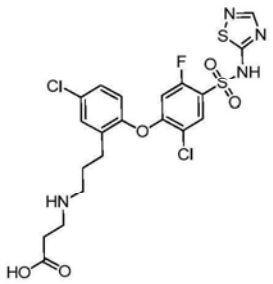
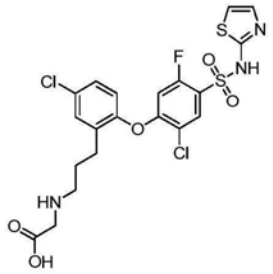
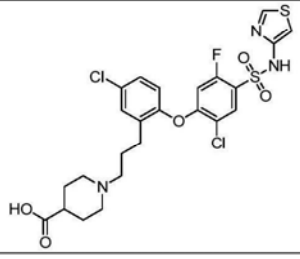
[0173]

实例	化合物结构	化学名
1		3-（4-（2-（4-（N-（1,2,4-噻二唑-5-基）氨磺酰基）-2-氯-5-氟苯氧基）-5-氯苯基）吡啶酰胺基）丙酸
2		2-（4-（2-（4-（N-（1,2,4-噻二唑-5-基）氨磺酰基）-2-氯-5-氟苯氧基）-5-氯苯基）吡啶酰胺基）乙酸
3		5-（4-（2-（4-（N-（1,2,4-噻二唑-5-基）氨磺酰基）-2-氯-5-氟苯氧基）-5-氯苯基）吡啶酰胺基）戊酸
4		4-（4-（2-（4-（N-（1,2,4-噻二唑-5-基）氨磺酰基）-2-氯-5-氟苯氧基）-5-氯苯基）吡啶酰胺基）丁酸

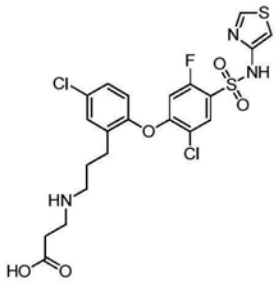
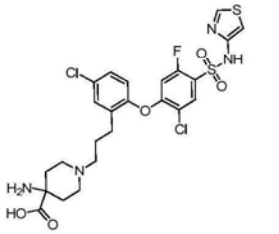
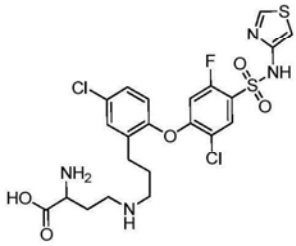
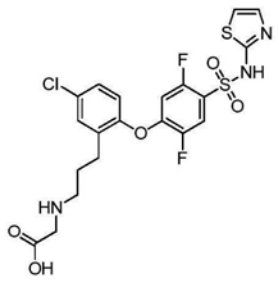
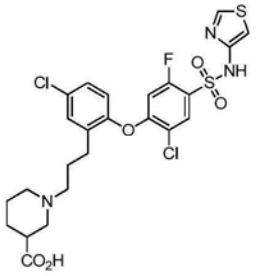
[0174]

实例	化合物结构	化学名
5		2-（4-（2-（4-（N-（1,2,4-噻二唑-5-基）氨磺酰基）-2-氯-5-氟苯氧基）-5-氯苯基）吡啶酰胺基）丙酸
6		（R）-2-（4-（2-（4-（N-（1,2,4-噻二唑-5-基）氨磺酰基）-2-氯-5-氟苯氧基）-5-氯苯基）吡啶酰胺基）丙酸
7		2-（6-（2-（4-（N-（1,2,4-噻二唑-5-基）氨磺酰基）-2-氯-5-氟苯氧基）-5-氯苯基）吡啶酰胺基）乙酸
8		（S）-2-（4-（2-（4-（N-（1,2,4-噻二唑-5-基）氨磺酰基）-2-氯-5-氟苯氧基）-5-氯苯基）吡啶酰胺基）丙酸
9		3-（4-（2-（4-（N-（1,2,4-噻二唑-5-基）氨磺酰基）-2-氰基苯氧基）-5-氯苯基）吡啶酰胺基）丙酸

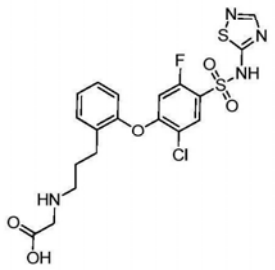
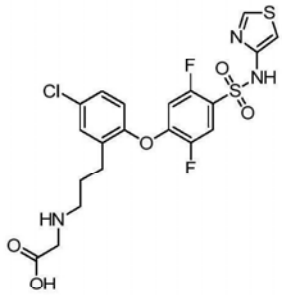
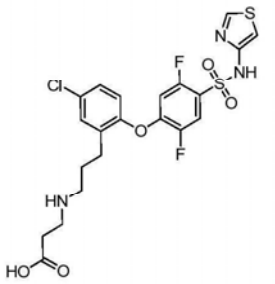
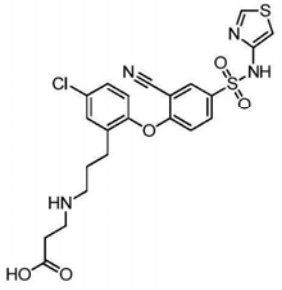
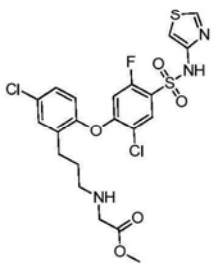
[0175]

实例	化合物结构	化学名
10		3-（4-（2-（4-（N-（1,2,4-噻二唑-5-基）氨磺酰基）-2,5-二氟苯氧基）-5-氯苯基）吡啶酰胺基）丙酸
11		2-（（3-（5-氯-2-（2-氯-5-氟-4-（N-（噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）氨基）乙酸
12		3-（（3-（2-（4-（N-（1,2,4-噻二唑-5-基）氨磺酰基）-2-氯-5-氟苯氧基）-5-氯苯基）丙基）氨基）丙酸
13		2-（（3-（5-氯-2-（2-氯-5-氟-4-（N-（噻唑-2-基）氨磺酰基）苯氧基）苯基）丙基）氨基）乙酸
14		1-（3-（5-氯-2-（2-氯-5-氟-4-（N-（噻唑-4-基）氨磺酰基）苯氧基）苯基）丙基）哌啶）-4-羧酸

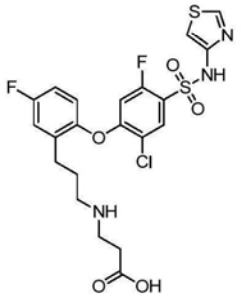
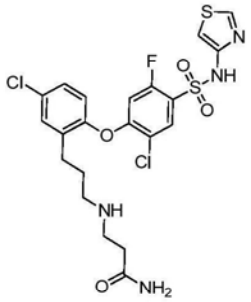
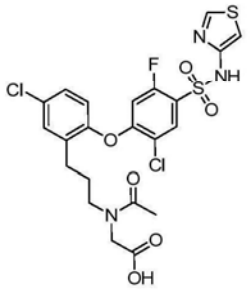
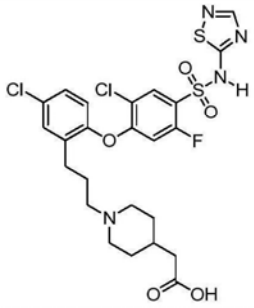
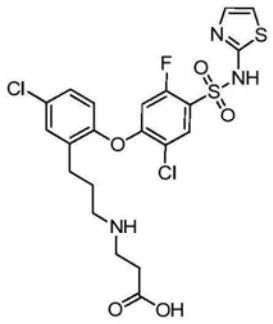
[0176]

实例	化合物结构	化学名
15		3-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)丙酸
16		4-氨基-1-(3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)哌啶)-4-羧酸
17		2-氨基-4-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)丁酸
18		2-((3-(5-氯-2-(2,5-二氟-4-(N-(噻唑-2-基)氨磺酰基)苯氧基)苯基)丙基)氨基)乙酸
19		1-(3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)哌啶)-3-羧酸

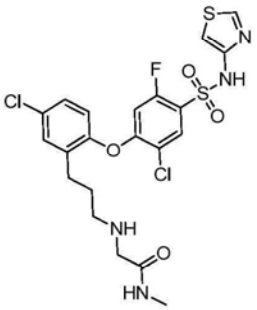
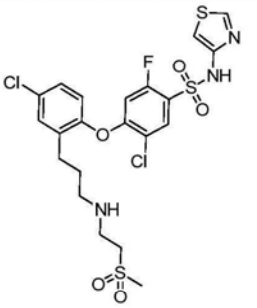
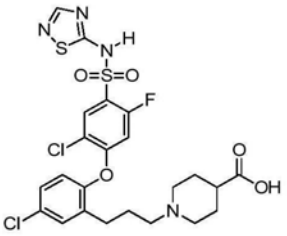
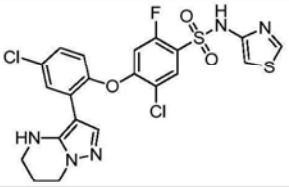
[0177]

实例	化合物结构	化学名
20		2-((3-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)苯基)丙基)氨基)乙酸
21		2-((3-(5-氯-2-(2,5-二氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)乙酸
22		3-((3-(5-氯-2-(2,5-二氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)丙酸
23		3-((3-(5-氯-2-(2-氰基-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)丙酸
24		甲基 2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)乙酸酯

[0178]

实例	化合物结构	化学名
25		3-((3-(2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)-5-氟苯基)丙基)氨基)丙酸
26		3-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)丙酰胺
27		2-(N-(3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)乙酰氨基)乙酸
28		2-(1-(3-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)丙基)哌啶-4-基)乙酸
29		3-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-2-基)氨磺酰基)苯氧基)苯基)丙基)氨基)丙酸

[0179]

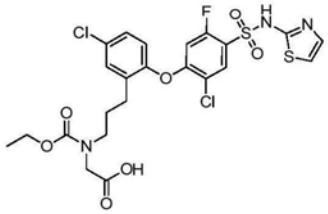
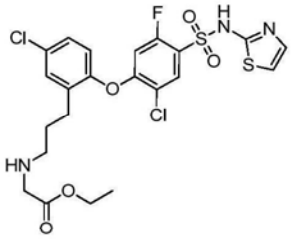
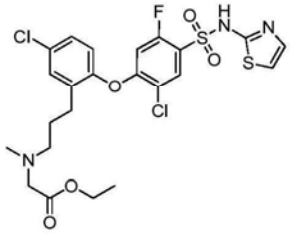
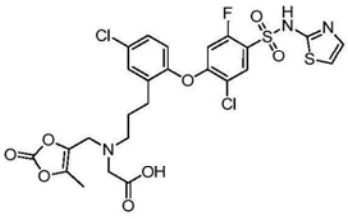
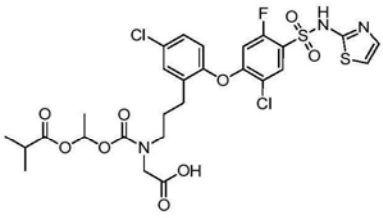
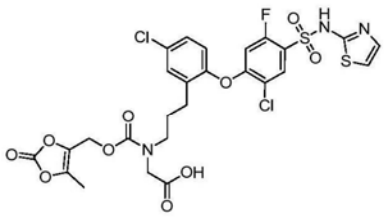
实例	化合物结构	化学名
30		2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)-N-甲基乙酰胺
31		5-氯-4-(4-氯-2-(3-((2-(甲磺酰基)乙基)氨基)丙基)苯氧基)-2-氟-N-(噻唑-4-基)苯磺酰胺
32		1-(3-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)丙基)哌啶-4-羧酸
33		5-氯-4-(4-氯-2-(4,5,6,7-四氢吡唑并[1,5-α]嘧啶-3-基)苯氧基)-2-氟-N-(噻唑-4-基)苯磺酰胺

[0180] *化学名由 ChemDraw Ultra,12.0 版本自动生成。

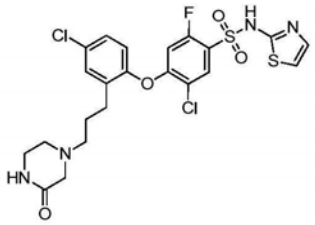
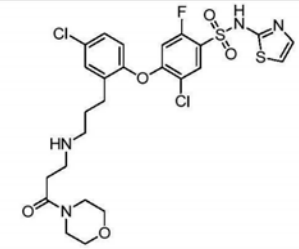
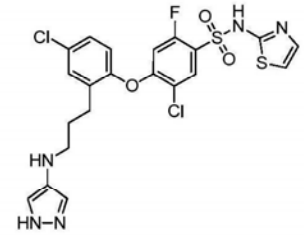
[0181] 在某些实施方式中,式(I)的化合物是选自由表 2 中的化合物或可药用的盐、或其立体异构或互变异构形式组成的组的化合物。

[0182] 表 2

[0183]

可预见的实例	化合物结构	化学名*
34		2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-2-基)氨磺酰基)苯氧基)苯基)丙基)(乙酯基)氨基)乙酸
35		乙基 2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-2-基)氨磺酰基)苯氧基)苯基)丙基)氨基)乙酸酯
36		乙基 2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-2-基)氨磺酰基)苯氧基)苯基)丙基)(甲基)氨基)乙酸酯
37		2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-2-基)氨磺酰基)苯氧基)苯基)丙基)((5-甲基-2-氧代-1,3-二氧杂环戊烯-4-基)甲基)氨基)乙酸
38		2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-2-基)氨磺酰基)苯氧基)苯基)丙基)((1-(异丁酰氧基)乙氧基)羰基)氨基)乙酸
39		2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-2-基)氨磺酰基)苯氧基)苯基)丙基)(((5-甲基-2-氧代-1,3-二氧杂环戊烯-4-基)甲氧基)羰基)氨基)乙酸

[0184]

可预见的实例	化合物结构	化学名*
40		5-氯-4-（4-氯-2-（3-（3-氧代哌嗪-1-基）丙基）苯氧基）-2-氟-N-（噻唑-2-基）苯磺酰胺
41		5-氯-4-（4-氯-2-（3-（（3-吗啉基-3-氧代丙基）氨基）丙基）苯氧基）-2-氟-N-（噻唑-2-基）苯磺酰胺
42		4-（2-（3-（（1H-吡唑-4-基）氨基）丙基）-4-氯苯氧基）-5-氯-2-氟-N-（噻唑-2-基）苯磺酰胺

[0185] *化学名由 ChemDraw Ultra,12.0 版本自动生成。

[0186] 对于本公开的提议,表 1 和表 2 用于定义与具体名称相关的具体结构。每当在本公开中或权利要求书中叙述具体名称时,与具体名称相关的化学结构应当是表 1 或表 2 中指定的结构。

[0187] 在具体实施方式中,式 (I) 的化合物是以下化合物 :

[0188] 2-(4-(2-(4-(N-(1,2,4- 噻二唑 -5- 基) 氨磺酰基)-2- 氯 -5- 氟苯氧基)-5- 氯苯基) 吡啶酰胺基) 乙酸、

[0189] 3-(4-(2-(4-(N-(1,2,4- 噻二唑 -5- 基) 氨磺酰基)-2- 氯 -5- 氟苯氧基)-5- 氯苯基) 吡啶酰胺基) 丙酸、

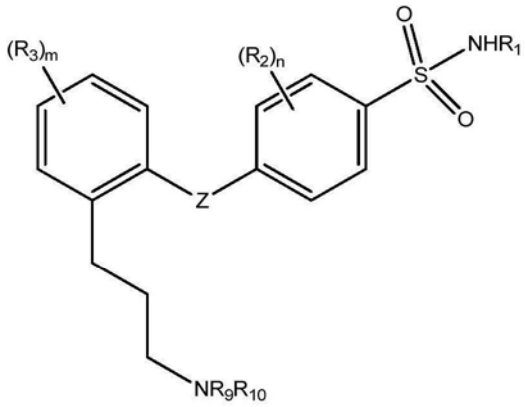
[0190] 2-(4-(2-(4-(N-(1,2,4- 噻二唑 -5- 基) 氨磺酰基)-2- 氯 -5- 氟苯氧基)-5- 氯苯基) 吡啶酰胺基) 丙酸、或

[0191] 3-((3-(2-(4-(N-(1,2,4- 噻二唑 -5- 基) 氨磺酰基)-2- 氯 -5- 氟苯氧基)-5- 氯苯基) 丙基) 氨基) 丙酸 ;

[0192] 或可药用的盐,或其立体异构形式或互变异构形式。

[0193] 本文进一步提供式 (Ia) 的化合物,

[0194]



式（Ia）

[0195] 或可药用的盐，或其立体异构形式或互变异构形式，其中：

[0196] Z 是 -O- 或 -S-；

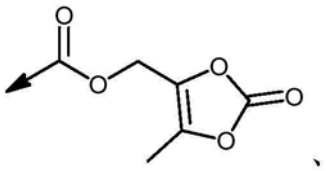
[0197] R_1是部分未饱和的或芳香族 5 元杂环或 6 元杂环；

[0198] R_2在每次出时独立地为 -F、-Cl、-Br、-CH_3或 -CN；

[0199] R_3在每次出时独立地为-H、-F、-Cl、-Br、-CF_3、-OCF_3、-CN、(C_1-C_{12}) 烷基、或 (C_1-C_{12}) 烷氧基；

[0200] R_9是 (C_1-C_6) 烷基、(C_3-C_8) 环烷基、吡唑基或吡啶基；其中，R_9任选地进一步被选自由 -COOH、-$COOR_{11}$、-$CONR_{11}R_{12}$、-SO_2R_{11}、-$SO_2NR_{11}R_{12}$、-OH、-CN、-OR_{11}、和 -$NR_{11}R_{12}$组成的组的 1 或 2 个取代基取代；其中，R_{11}和 R_{12}可以形成 6 元杂环烷基环；

[0201] R_{10}是 R_{11}、-COR_{11}、-$COOR_{11}$、-SO_2R_{11}、5- 甲基 -2- 氧代 -1,3- 二氧杂环戊烯 -4- 基、



-COO-CH(CH_3)OCOCH(CH_3)$_2$；或 R_9和 R_{10}一起形成哌嗪酮或 4 至 8 元杂环烷基环，其中所述杂环烷基环被选自由 -COOH、-$COOR_{11}$、-CH_2-$COOR_{11}$、-OH、-NH_2、-CN、和 (C_1-C_8) 烷氧基组成的组的 1 或 2 个取代基取代；

[0202] R_{11}和 R_{12}独立地是 H 或 (C_1-C_6) 烷基，可任选地被 4 至 8 元杂环烷基环取代；并且

[0203] m 和 n 均独立地是 1、2、3 或 4。

[0204] 在具体实施方式中，式 (Ia) 的化合物是 R_1是芳香族 5 元杂环或 6 元杂环的化合物，其具有独立地选自由 N、O、和 S 组成的组的 1-3 个杂原子。

[0205] 在具体实施方式中，式 (Ia) 的化合物是 R_1为吡啶基或嘧啶基的化合物。

[0206] 在具体实施方式中，式 (Ia) 的化合物是 R_1是具有 1 或 2 个氮原子并且任选地具有 1 或 2 个硫原子的芳香族 5 元杂环的化合物。在具体实施方式中，式 (Ia) 的化合物是 R_1为噻唑基、异噻唑基、或噻二唑基的化合物。在具体实施方式中，式 (Ia) 的化合物是 R_1为噻唑基的化合物。在具体实施方式中，式 (Ia) 的化合物是 R_1为 1,2,4- 噻二唑 -5- 基的化合物。

[0207] 在具体实施方式中，式 (Ia) 的化合物是 R_2在每次出时独立地为 -F 或 -Cl 的化合物。

[0208] 在具体实施方式中，式 (Ia) 的化合物是 n 为 1、2、或 3 的化合物。在具体实施方式中，式 (Ia) 的化合物是 n 为 2 的化合物。

[0209] 在具体实施方式中，式 (Ia) 的化合物是 Z 为 -O- 的化合物。

[0210] 在具体实施方式中，式 (Ia) 的化合物是 R_3 在每次出时独立地为 -H、-F、-Cl、或 -Br 的化合物。在具体实施方式中，式 (Ia) 的化合物是 R_3 为 -H 或 -Cl 的化合物。在具体实施方式中，式 (Ia) 的化合物是 R_3 为 -Cl 的化合物。

[0211] 在具体实施方式中，式 (Ia) 的化合物是 m 为 1、2、或 3 的化合物。在具体实施方式中，式 (Ia) 的化合物是 m 为 1 的化合物。

[0212] 在具体实施方式中，式 (Ia) 的化合物是 R_9 为 (C_1-C_6) 烷基的化合物；其中，R_9 任选地进一步被选自由 -COOH、-COOMe、-$CONH_2$、和 NH_2 组成的组的 1 或 2 个取代基取代。在具体实施方式中，式 (Ia) 的化合物是 R_9 是甲基或乙基的化合物。在具体实施方式中，式 (Ia) 的化合物是 R_9 进一步被 -COOH 取代的化合物。

[0213] 在具体实施方式中，式 (Ia) 的化合物是 R_{10} 为 -H、-COMe、-COOEt 的化合物。在具体实施方式中，式 (Ia) 的化合物是 R_{10} 为 -H 或 -COMe 的化合物。在具体实施方式中，式 (Ia) 的化合物是 R_{10} 为 -H 的化合物。

[0214] 在具体实施方式中，式 (Ia) 的化合物是 R_9 和 R_{10} 一起形成 4 至 8 元杂环烷基环的化合物，其中，所述杂环烷基环由选自由 -COOH、-COOMe、-COOEt、CH_2-COOH、和 -NH_2 组成的组的 1 或 2 个基团取代。在具体实施方式中，式 (Ia) 的化合物是 R_9 和 R_{10} 一起形成 4 至 8 元杂环烷基环的化合物，其中，所述杂环烷基环由选自由 -COOH、CH_2-COOH、和 -NH_2 组成的组的 1 或 2 个基团取代。

[0215] 在具体实施方式中，式 (Ia) 的化合物是 R_9 和 R_{10} 一起形成由选自由 -COOH、-COOMe、-COOEt、CH_2-COOH、-CH_2-COOMe、-CH_2-COOEt 和 -NH_2 组成的组的 1 或 2 个基团取代的哌啶的化合物。在具体实施方式中，式 (Ia) 的化合物是 R_9 和 R_{10} 一起形成由选自由 -COOH、CH_2-COOH、和 -NH_2 组成的组的 1 或 2 个基团取代的哌啶的化合物。

[0216] 在具体实施方式中，式 (Ia) 选自由以下各项组成的组：

[0217] 2-((3-(5- 氯 -2-(2- 氯 -5- 氟 -4-(N-(噻唑 -4- 基) 氨磺酰基) 苯氧基) 苯基) 丙基) 氨基) 乙酸、

[0218] 3-((3-(2-(4-(N-(1,2,4- 噻二唑 -5- 基) 氨磺酰基)-2- 氯 -5- 氟苯氧基)-5- 氯苯基) 丙基) 氨基) 丙酸、

[0219] 2-((3-(5- 氯 -2-(2- 氯 -5- 氟 -4-(N-(噻唑 -2- 基) 氨磺酰基) 苯氧基) 苯基) 丙基) 氨基) 乙酸、

[0220] 1-(3-(5- 氯 -2-(2- 氯 -5- 氟 -4-(N-(噻唑 -4- 基) 氨磺酰基) 苯氧基) 苯基) 丙基) 哌啶)-4- 羧酸、

[0221] 3-((3-(5- 氯 -2-(2- 氯 -5- 氟 -4-(N-(噻唑 -4- 基) 氨磺酰基) 苯氧基) 苯基) 丙基) 氨基) 丙酸、

[0222] 4- 氨基 -1-(3-(5- 氯 -2-(2- 氯 -5- 氟 -4-(N-(噻唑 -4- 基) 氨磺酰基) 苯氧基) 苯基) 丙基) 哌啶)-4- 羧酸、

[0223] 2- 氨基 -4-((3-(5- 氯 -2-(2- 氯 -5- 氟 -4-(N-(噻唑 -4- 基) 氨磺酰基) 苯氧基) 苯基) 丙基) 氨基) 丁酸、

[0224] 2-((3-(5-氯-2-(2,5-二氟-4-(N-(噻唑-2-基)氨磺酰基)苯氧基)苯基)丙基)氨基)乙酸、

[0225] 1-(3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)哌啶)-3-羧酸、

[0226] 2-((3-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)苯基)丙基)氨基)乙酸、

[0227] 2-((3-(5-氯-2-(2,5-二氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)乙酸、

[0228] 3-((3-(5-氯-2-(2,5-二氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)丙酸、

[0229] 3-((3-(5-氯-2-(2-氰基-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)丙酸、

[0230] 甲基2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)乙酸酯、

[0231] 3-((3-(2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)-5-氟苯基)丙基)氨基)丙酸、

[0232] 3-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)丙酰胺、

[0233] 2-(N-(3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)乙酰氨基)乙酸、

[0234] 2-(1-(3-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)丙基)哌啶-4-基)乙酸、

[0235] 3-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-2-基)氨磺酰基)苯氧基)苯基)丙基)氨基)丙酸、

[0236] 2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)-N-甲基乙酰胺、

[0237] 5-氯-4-(4-氯-2-(3-((2-(甲磺酰基)乙基)氨基)丙基)苯氧基)-2-氟-N-(噻唑-4-基)苯磺酰胺、和

[0238] 1-(3-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)丙基)哌啶-4-羧酸；

[0239] 或可药用的盐，或其立体异构形式或互变异构形式。

[0240] 在具体实施方式中，式(Ia)选自包括以下各项的组：

[0241] 2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-2-基)氨磺酰基)苯氧基)苯基)丙基)(乙酯基)氨基)乙酸、

[0242] 乙基2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-2-基)氨磺酰基)苯氧基)苯基)丙基)氨基)乙酸酯、

[0243] 乙基2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-2-基)氨磺酰基)苯氧基)苯基)丙基)(甲基)氨基)乙酸酯、

[0244] 2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-2-基)氨磺酰基)苯氧基)苯基)

丙基)((5-甲基-2-氧代-1,3-二氧杂环戊烯-4-基)甲基)氨基)乙酸、

[0245] 2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-2-基)氨磺酰基)苯氧基)苯基)丙基)((1-(异丁酰氧基)乙氧基)羰基)氨基)乙酸、

[0246] 2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-2-基)氨磺酰基)苯氧基)苯基)丙基)(((5-甲基-2-氧代-1,3-二氧杂环戊烯-4-基)甲氧基)羰基)氨基)乙酸、

[0247] 5-氯-4-(4-氯-2-(3-(3-氧代哌嗪-1-基)丙基)苯氧基)-2-氟-N-(噻唑-2-基)苯磺酰胺、

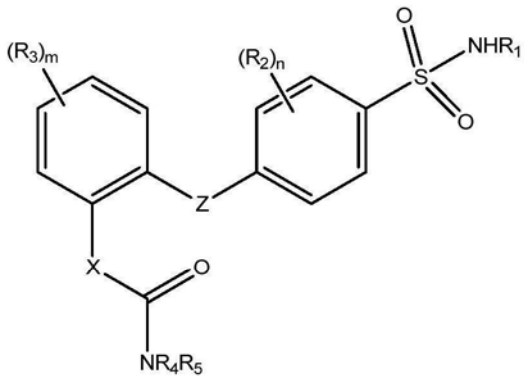
[0248] 5-氯-4-(4-氯-2-(3-((3-吗啉基-3-氧代丙基)氨基)丙基)苯氧基)-2-氟-N-(噻唑-2-基)苯磺酰胺、和

[0249] 4-(2-(3-((1H-吡唑-4-基)氨基)丙基)-4-氯苯氧基)-5-氯-2-氟-N-(噻唑-2-基)苯磺酰胺;

[0250] 或可药用的盐,或其立体异构形式或互变异构形式。

[0251] 本文提供了式(Ib)的化合物,

[0252]



式(Ib)

[0253] 或可药用的盐,或其立体异构形式或互变异构形式,其中:

[0254] Z是-O-或-S-;

[0255] X是(C_6-C_{10})芳基或5元杂芳基或6元杂芳基;

[0256] R_1是部分未饱和的或芳香族的5元杂环或6元杂环;

[0257] R_2在每次出时独立地为-F、-Cl、-Br、-CH_3或-CN;

[0258] R_3在每次出时独立地为-H、-F、-Cl、-Br、-CF_3、-OCF_3、-CN、(C_1-C_{12})烷基、或(C_1-C_{12})烷氧基;

[0259] R_4和R_5均独立地是H、(C_1-C_9)烷基、(C_4-C_{12})环烷基或R_4和R_5一起形成5至7元杂环烷基环;前提条件是:

[0260] R_4和R_5都不是H;并且

[0261] R_4和R_5中至少一个独立地被或R_4和R_5一起形成的所述杂环烷基环被选自由-CO_2H、-CO_2R_6、-CN、-OH、-$CONR_7R_8$和-NR_7R_8组成的组的1或2个取代基取代;其中:

[0262] R_6是(C_1-C_{12})烷基;

[0263] R_7和R_8各自独立地是H、(C_1-C_{12})烷基,或R_7和R_8一起形成4至7元杂环烷基环;并且

[0264] m和n均独立地是1、2、3或4。

[0265] 在具体实施方式中，式 (Ib) 的化合物是 R_1是芳香族 5 元杂环或 6 元杂环的化合物，其具有独立地选自由 N、O、和 S 组成的组的 1-3 个杂原子。

[0266] 在具体实施方式中，式 (Ib) 的化合物是 R_1为吡啶基或嘧啶基的化合物。

[0267] 在具体实施方式中，式 (Ib) 的化合物是 R_1是具有 1 或 2 个氮原子并且任选地具有 1 或 2 个硫原子的芳香族 5 元杂环的化合物。在具体实施方式中，式 (Ib) 的化合物是 R_1为噻唑基、异噻唑基、或噻二唑基的化合物。在具体实施方式中，式 (Ib) 的化合物是 R_1为噻唑基的化合物。在具体实施方式中，式 (Ib) 的化合物是 R_1为 1,2,4- 噻二唑 -5- 基的化合物。

[0268] 在具体实施方式中，式 (Ib) 的化合物是 R_2在每次出时独立地为 -F 或 -Cl 的化合物。

[0269] 在具体实施方式中，式 (Ib) 的化合物是 n 为 1、2、或 3 的化合物。在具体实施方式中，式 (Ib) 的化合物是 n 为 2。

[0270] 在具体实施方式中，式 (Ib) 的化合物是 Z 为 -O- 的化合物。

[0271] 在具体实施方式中，式 (Ib) 的化合物是 R_3在每次出时独立地为 -F、-Cl、或 -Br 的化合物。在具体实施方式中，式 (Ib) 的化合物是 R_3为 -H 或 -Cl 的化合物。在具体实施方式中，式 (Ib) 的化合物是 R_3为 -Cl 的化合物。

[0272] 在具体实施方式中，式 (Ib) 的化合物是 m 为 1、2、或 3 的化合物。在具体实施方式中，式 (Ib) 的化合物是 m 为 1 的化合物。

[0273] 在具体实施方式中，式 (Ib) 的化合物是 X 为 5 元杂芳基或 6 元杂芳基的化合物。在具体实施方式中，式 (Ib) 的化合物是 X 为吡啶基或嘧啶基的化合物。在具体实施方式中，式 (Ib) 的化合物是 X 为吡啶基的化合物。

[0274] 在具体实施方式中，式 (Ib) 的化合物是 R_4为 H 且 R_5为 (C_1-C_9) 烷基的化合物。

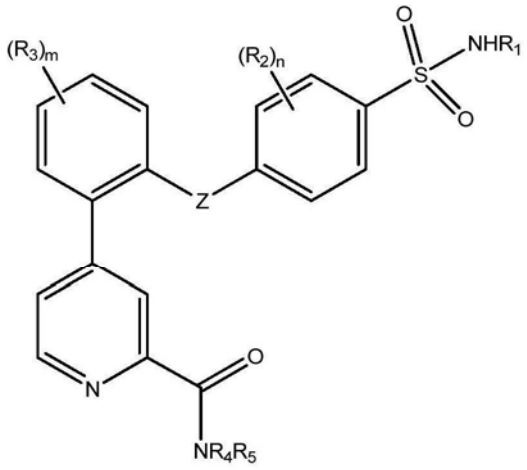
[0275] 在具体实施方式中，式 (Ib) 的化合物是 R_5为被选自由 $-CO_2H$、$-CO_2R_6$、和 $-CONR_7R_8$ 组成的组的 1 或 2 个取代基取代的甲基或乙基的化合物。

[0276] 在具体实施方式中，式 (Ib) 的化合物是 R_6为 (C_1-C_6) 烷基的化合物。

[0277] 在具体实施方式中，式 (Ib) 的化合物是 R_5是由 $-CO_2H$ 取代的甲基或乙基的化合物。

[0278] 本文提供了式 (Ic) 的化合物，

[0279]



式（Ic）

[0280] 或可药用的盐，或其立体异构形式或互变异构形式，其中：

[0281] Z 是 -O- 或 -S-；

[0282] R_1是部分未饱和的或芳香族的 5 元杂环或 6 元杂环；

[0283] R_2在每次出时独立地为 -F、-Cl、-Br、$-CH_3$或 -CN；

[0284] R_3在每次出时独立地为 -H、-F、-Cl、-Br、$-CF_3$、$-OCF_3$、-CN、(C_1-C_{12}) 烷基、或 (C_1-C_{12}) 烷氧基；

[0285] R_4和 R_5均独立地是 H、(C_1-C_9) 烷基、(C_4-C_{12}) 环烷基或 R_4和 R_5一起形成 5 至 7 元杂环烷基环；前提条件是：

[0286] R_4和 R_5都不是 H；并且

[0287] R_4和 R_5中至少一个独立地被或 R_4和 R_5一起形成的所述杂环烷基环被选自由 $-CO_2H$、$-CO_2R_6$、-CN、-OH、$-CONR_7R_8$和 $-NR_7R_8$组成的组的 1 或 2 个取代基取代；其中：

[0288] R_6是 (C_1-C_{12}) 烷基；

[0289] R_7和 R_8各自独立地是 H、(C_1-C_{12}) 烷基，或 R_7和 R_8一起形成 4 至 7 元杂环烷基环；并且

[0290] m 和 n 均独立地是 1、2、3 或 4。

[0291] 在具体实施方式中，式 (Ic) 的化合物是 R_1为芳香族 5 元杂环或 6 元杂环的化合物，其具有独立地选自由 N、O、和 S 组成的组的 1-3 个杂原子。

[0292] 在具体实施方式中，式 (Ic) 的化合物是 R_1为吡啶基或嘧啶基的化合物。

[0293] 在具体实施方式中，式 (Ic) 的化合物是 R_1是芳香族 5 元杂环的化合物，其具有 1 或 2 个氮原子并且任选地 1 或 2 个硫原子。在具体实施方式中，式 (Ic) 的化合物是 R_1为噻唑基、异噻唑基、或噻二唑基的化合物。在具体实施方式中，式 (Ic) 的化合物是 R_1为噻唑基的化合物。在具体实施方式中，式 (Ic) 的化合物是 R_1为 1,2,4- 噻二唑 -5- 基的化合物。

[0294] 在具体实施方式中，式 (Ic) 的化合物是 R_2在每次出时独立地为 -F 或 -Cl 的化合物。

[0295] 在具体实施方式中，式 (Ic) 的化合物是 n 为 1、2、或 3 的化合物。在具体实施方式中，式 (Ic) 的化合物是 n 为 2 的化合物。

[0296] 在具体实施方式中，式 (Ic) 的化合物是 Z 为 -O- 的化合物。

[0297] 在具体实施方式中，式（Ic）的化合物是R_3在每次出时独立地为-F、-Cl、或-Br的化合物。在具体实施方式中，式（I）的化合物是R_3为-H或-Cl的化合物。在具体实施方式中，式（Ic）的化合物是R_3为-Cl的化合物。

[0298] 在具体实施方式中，式（Ic）的化合物是m为1、2、或3的化合物。在具体实施方式中，式（Ic）的化合物是m为1的化合物。

[0299] 在具体实施方式中，式（Ic）的化合物是X为5元杂芳基或6元杂芳基的化合物。在具体实施方式中，式（Ic）的化合物是X为吡啶基或嘧啶基的化合物。在具体实施方式中，式（Ic）的化合物是X为吡啶基的化合物。

[0300] 在具体实施方式中，式（Ic）的化合物是R_4为H且R_5为（C_1-C_9）烷基的化合物。

[0301] 在具体实施方式中，式（Ic）的化合物是R_5为被选自由-CO_2H、-CO_2R_6、和-$CONR_7R_8$组成的组的1或2个取代基取代的甲基或乙基的化合物。

[0302] 在具体实施方式中，式（Ic）的化合物是R_6为（C_1-C_6）烷基的化合物。

[0303] 在具体实施方式中，式（Ic）的化合物是R_5为被-CO_2H取代的甲基或乙基的化合物。

[0304] 在具体实施方式中，式（Ic）选自由以下各项组成的组：

[0305] 3-(4-(2-(4-(N-(1,2,4-噻二唑-5-基）氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基）吡啶酰胺基）丙酸、

[0306] 2-(4-(2-(4-(N-(1,2,4-噻二唑-5-基）氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基）吡啶酰胺基）乙酸、

[0307] 5-(4-(2-(4-(N-(1,2,4-噻二唑-5-基）氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基）吡啶酰胺基）戊酸、

[0308] 4-(4-(2-(4-(N-(1,2,4-噻二唑-5-基）氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基）吡啶酰胺基）丁酸、

[0309] 2-(4-(2-(4-(N-(1,2,4-噻二唑-5-基）氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基）吡啶酰胺基）丙酸、

[0310] (R)-2-(4-(2-(4-(N-(1,2,4-噻二唑-5-基）氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基）吡啶酰胺基）丙酸、

[0311] (S)-2-(4-(2-(4-(N-(1,2,4-噻二唑-5-基）氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基）吡啶酰胺基）丙酸、

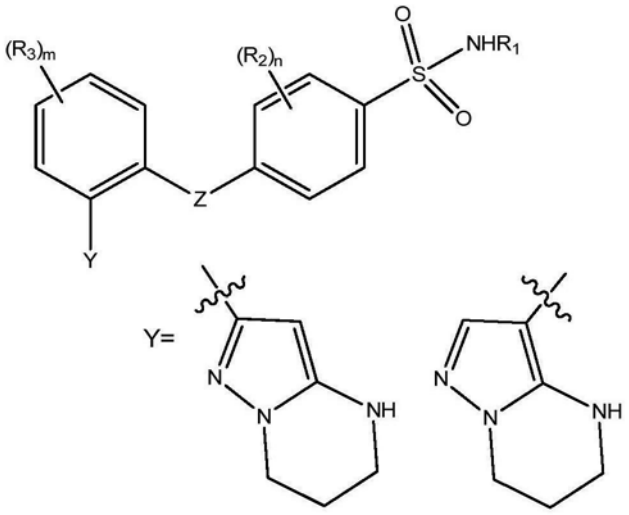
[0312] 3-(4-(2-(4-(N-(1,2,4-噻二唑-5-基）氨磺酰基)-2-氰基苯氧基)-5-氯苯基）吡啶酰胺基）丙酸、和

[0313] 3-(4-(2-(4-(N-(1,2,4-噻二唑-5-基）氨磺酰基)-2,5-二氟苯氧基)-5-氯苯基）吡啶酰胺基）丙酸、或

[0314] 可药用的盐，或其立体异构形式或互变异构形式。

[0315] 本文提供了式（Id）的化合物，

[0316]



式（Id）

[0317] 或可药用的盐，或其立体异构形式或互变异构形式，其中：

[0318] Y 是 4,5,6,7- 四氢吡唑并 [1,5- α] 嘧啶 -(2- 基或 3- 基）；

[0319] Z 是 -O- 或 -S-；

[0320] R_1是部分未饱和的或芳香族 5 元杂环或 6 元杂环；

[0321] R_2在每次出时独立地为 -F、-Cl、-Br、$-CH_3$或 -CN；

[0322] R_3在每次出时独立地为 -H、-F、-Cl、-Br、$-CF_3$、$-OCF_3$、-CN、(C_1-C_{12}) 烷基、或 (C_1-C_{12}) 烷氧基；和

[0323] m 和 n 均独立地是 1、2、3 或 4。

[0324] 在某些实施方式中，式 (Id) 的化合物是 Y 为 4,5,6,7- 四氢吡唑并 [1,5- α] 嘧啶 -(2- 基或 3- 基）的化合物。在具体实施方式中，式 (Id) 的化合物是 Y 为 4,5,6,7- 四氢吡唑并 [1,5- α] 嘧啶 -3- 基）的化合物。

[0325] 在具体实施方式中，式 (Id) 的化合物是 R_1为芳香 5 元杂环或 6 元杂环的化合物，其具有独立地选自由 N、O、和 S 组成的组的 1-3 个杂原子。

[0326] 在具体实施方式中，式 (Id) 的化合物是 R_1为吡啶基或嘧啶基的化合物。

[0327] 在具体实施方式中，式 (Id) 的化合物是 R_1为芳香 5 元杂环的化合物，其具有 1 或 2 个氮原子并且任选地具有 1 或 2 个硫原子。在具体实施方式中，式 (Id) 的化合物是 R_1为噻唑基、异噻唑基、或噻二唑基的化合物。在具体实施方式中，式 (Id) 的化合物是 R_1为噻唑基的化合物。在具体实施方式中，式 (Id) 的化合物是 R_1为 1,2,4- 噻二唑 -5- 基的化合物。

[0328] 在具体实施方式中，式 (Id) 的化合物是 R_2在每次出时独立地为 -F 或 -Cl 的化合物。

[0329] 在具体实施方式中，式 (Id) 的化合物是 n 为 1、2、或 3 的化合物。在具体实施方式中，式 (Id) 的化合物是 n 为 2 的化合物。

[0330] 在具体实施方式中，式 (Id) 的化合物是 Z 为 -O- 的化合物。

[0331] 在具体实施方式中，式 (Id) 的化合物是 R_3在每次出时独立地为 -F、-Cl、或 -Br 的化合物。在具体实施方式中，式 (Id) 的化合物是 R_3为 -H 或 -Cl 的化合物。在具体实施方式中，式 (Id) 的化合物是 R_3为 -Cl 的化合物。

[0332] 在具体实施方式中，式 (Id) 的化合物是 m 为 1、2、或 3 的化合物。在具体实施方式中，式 (Id) 的化合物是 m 为 1 的化合物。

[0333] 在具体实施方式中，式 (Id) 的化合物为 5- 氯 -4-(4- 氯 -2-(4,5,6,7- 四氢吡唑并 [1,5-α] 嘧啶 -3- 基) 苯氧基)-2- 氟 -N-(噻唑 -4- 基) 苯磺酰胺 ;或可药用的盐、或其立体异构形式或互变异构形式。

[0334] 还应当注意到，本文提供的化合物可以在一个或多个原子包含非自然比例的原子同位素。例如，化合物可以用放射性同位素，如例如氚 (^{3}H)、碘 -125(^{125}I)、硫 -35(^{35}S)、或碳 -14(^{14}C) 作放射性同位素标记，或可以同位素富集如氘 (^{2}H)、碳 13(^{13}C)、或氮 15(^{15}N)。如本文所用，“同位素异数体”是同位素富集的化合物。术语“同位素富集的”指的是具有不同于该原子的天然同位素组成的同位素组成的原子。“同位素富集的”也指的是含有不同于该原子的天然同位素组成的同位素组成的至少一个原子的化合物。术语“同位素组成”指的是代表给定原子的每种同位素的量。放射性同位素标记和同位素富集的化合物是可用作治疗剂，例如，癌症和炎症的治疗剂 ;研究试剂，例如，结合测定试剂 ;和诊断剂，例如，体内成像剂。本文描述的化合物的所有同位素变型，无论是否为放射性，旨在包含在本文提供的实施方式的范围内。在一些实施方式中，提供了化合物的同位素异数体，例如，同位素异数体为富含氘、碳 -13、或氮 -15 的化合物。

[0335] 在某些实施方式中，本文提供的化合物调节钠离子通道的活性，如电压依赖性钠离子通道。在更具体的实施方式中，这种电压依赖性钠离子通道是 NaV1.7(其 α 亚基由人基因 SCN9A 编码)。

[0336] 在某些实施方式中，本文提供的化合物比不存在该化合物的激活通道减少至少 10％、20％、30％、40％、50％、60％、70％、80％、90％、95％、98％、99％、或 100％，或在任意的列举的百分比范围之间 (例如，10-20％、10-30％、10-40％、20-30％、或 20-40％) 的范围内的穿过 NaV1.7 的钠离子通量。

[0337] 在某些实施方式中，本文提供的化合物比不存在该化合物的激活通道增加至少 10％、20％、30％、40％、50％、60％、70％、80％、90％、100％、250％、500％、750％或 1000％，或在任意的列举的百分比范围之间 (例如，10-20％、10-30％、10-40％、20-30％、或 20-40％) 的范围内的穿过 NaV1.7 的钠离子通量。

[0338] 在某些实施方式中，本文提供的化合物使 NaV1.7 对改变膜电位的响应不敏感使得通道比不存在该混合物的通道要求高至少 10％、20％、30％、40％、50％、60％、70％、80％、90％或 100％或在任意的列举的百分比范围之间 (例如，10-20％、10-30％、10-40％、20-30％、或 20-40％) 的范围内的膜电位来激活。

[0339] 在某些实施方式中，本文提供的化合物使 NaV1.7 对改变膜电位的响应敏感使得通道比不存在该混合物的通道要求低至少 10％、20％、30％、40％、50％、60％、70％、80％、90％或 100％或在任意的列举的百分比范围之间 (例如，10-20％、10-30％、10-40％、20-30％、或 20-40％) 的范围内的膜电位来激活。

[0340] 在某些实施方式中，本文提供的化合物在一个或多个下述状态中影响电压依赖性钠离子通道 (例如，NaV1.7) :去激活 (关闭)、激活 (开启) 或未激活 (关闭)。

[0341] 在某些实施方式中，本文提供的化合物影响电压依赖性钠离子通道 (例如，NaV1.7) 的激活、未激活或去激活。

[0342] 在某些实施方式中，本文提供的化合物特别地调控 NaV1.7，即，该化合物调控 NaV1.7 比另一个电压依赖性钠离子通道（例如，NaV1.1、NaV1.2、NaV1.3、NaV1.4、NaV1.5、NaV1.6、NaV1.8 和 / 或 NaV1.9）高至少 10％、20％、30％、40％、50％、60％、70％、80％、90％、100％、250％、500％、750％或 1000％的程度，或者比另一个电压依赖性钠通道高任意的列举的百分比（例如，10-20％、10-30％、10-40％、20-30％、或 20-40％）的程度。

[0343] 技术人员已知的任何试验可以用于测试本文提供的化合物对电压依赖性钠离子通道的效果。在某些实施方式中，使用细胞培养试验，在培养的细胞中重组表达电压依赖性钠离子通道。在某些更具体的实施方式中，表达了电压依赖性钠离子通道的 α 亚基，但是在同一细胞中不重组表达辅助蛋白。在具体实施方式中，SCN9A 和 SCN9B1 以及 SCN9B2 在同一细胞中共同表达。在其他实施方式中，表达了电压依赖性钠离子通道的 α 亚基，并且在同一细胞中共同表达至少一种辅助蛋白（例如，β 亚基）。

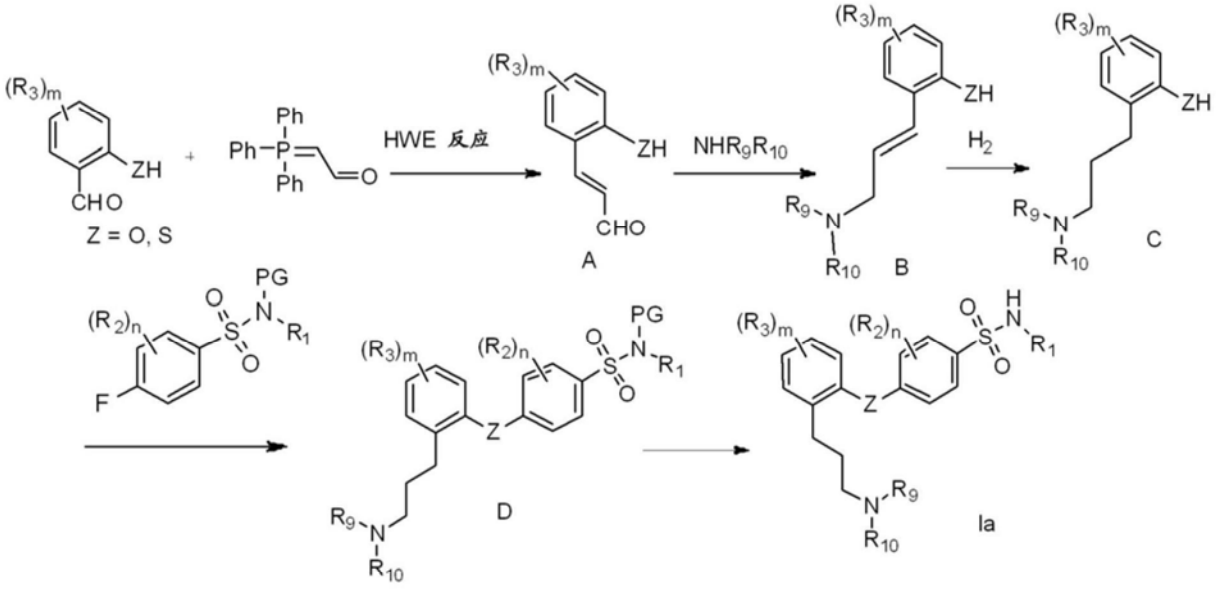
[0344] 在某些实施方式中，FDSS 膜电位试验可以用于测定电压依赖性钠离子通道的活性（参见下文题为“FDSS 膜电位体外试验”小节）。在其他实施方式中，使用直接测量膜电位。在某些实施方式中，使用膜片钳技术直接测量通过电压依赖性钠离子通道的电流。

[0345] 4.3 制备化合物的方法

[0346] 根据合成方案 1 合成式 (Ia) 的化合物。R_3取代的 2- 羟基苯甲醛或 2- 巯基苯在霍纳尔 - 沃兹沃思 - 埃蒙斯（“HWE”）条件下与甲酰甲基 - 三苯基膦反应得到中间产物 A，即：α，-β - 未饱和醛。中间产物 A 在还原胺化条件下通过使用例如硼氢化钠与 HNR_9R_{10}反应以得到中间产物 B。然后中间产物 B 通过在存在金属催化剂（如钯碳）的状态下使用例如氢气还原以得到中间产物 C。中间产物 C 在存在碱（如碳酸钾）的情况下与氟代苯基磺酰胺反应，以得到中间产物 D，其中磺酰胺氮可选地被基团（“PG”），如叔丁氧基羰基（“BOC”）或 2,4- 二甲氧基苄基保护。中间产物 D 的磺酰胺基团通过使用例如盐酸去保护以得到式 (Ia) 的化合物。

[0347] 方案 1

[0348]

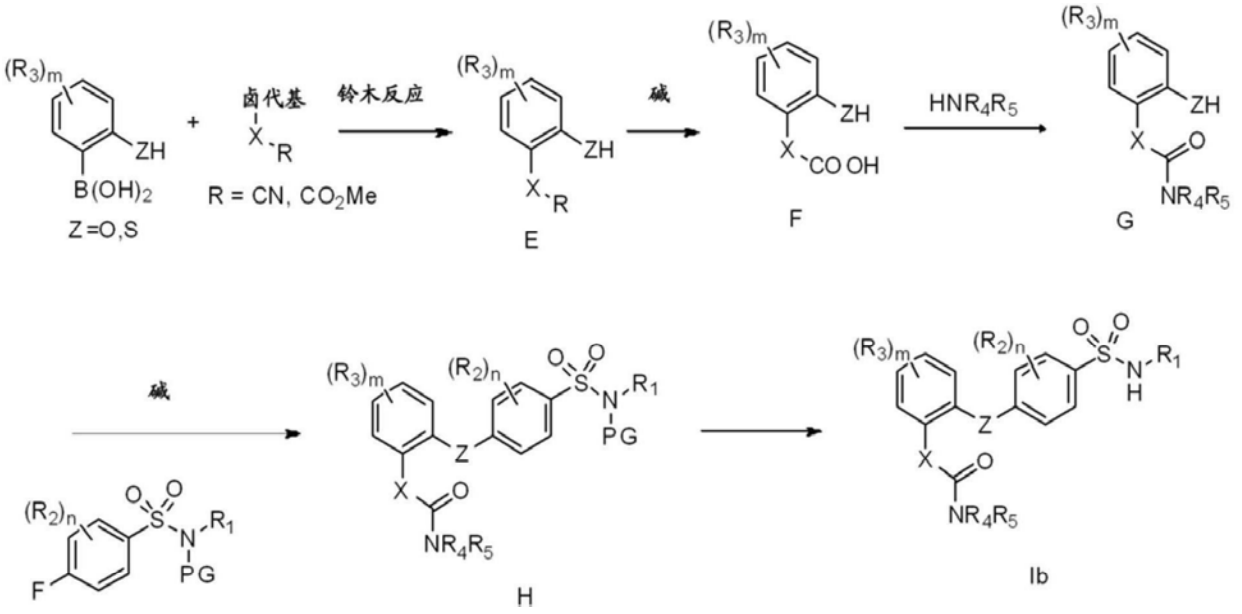


[0349] 根据合成方案 2 合成式 (Ib) 的化合物。在 R_3取代的 2- 羟基硼酸或 2- 巯基硼酸

和 X 的衍生物之间的铃木偶联反应提供中间产物 E，其中，X 是例如（C_6-C_{10}）芳基或 5 元杂芳基或 6 元杂芳基，如 4- 卤代甲基吡啶腈或 4- 卤代吡啶酯（例如，甲基吡啶），其中卤取代基是例如氯或溴取代基。中间产物 E 与碱（如氢氧化钾）反应以得到中间产物 F。中间产物 F 通过使用例如 1- 乙基 -3-(3- 二甲基氨丙基）碳二亚胺（“EDC”）和 1- 羟基 -1H- 苯并三唑（“HOBt”）与 NHR_4R_5 反应以形成酰胺中间产物 G。中间产物 G 在存在碱（如碳酸钾）的情况下与氟代苯基磺酰胺反应，以得到中间产物 H，其中磺酰胺氮可选地由基团，例如 BOC 或 2,4- 二甲氧基苄基保护。中间产物 H 的磺酰胺基团通过使用例如盐酸去保护以得到式（Ib）的化合物。

[0350] 方案 2

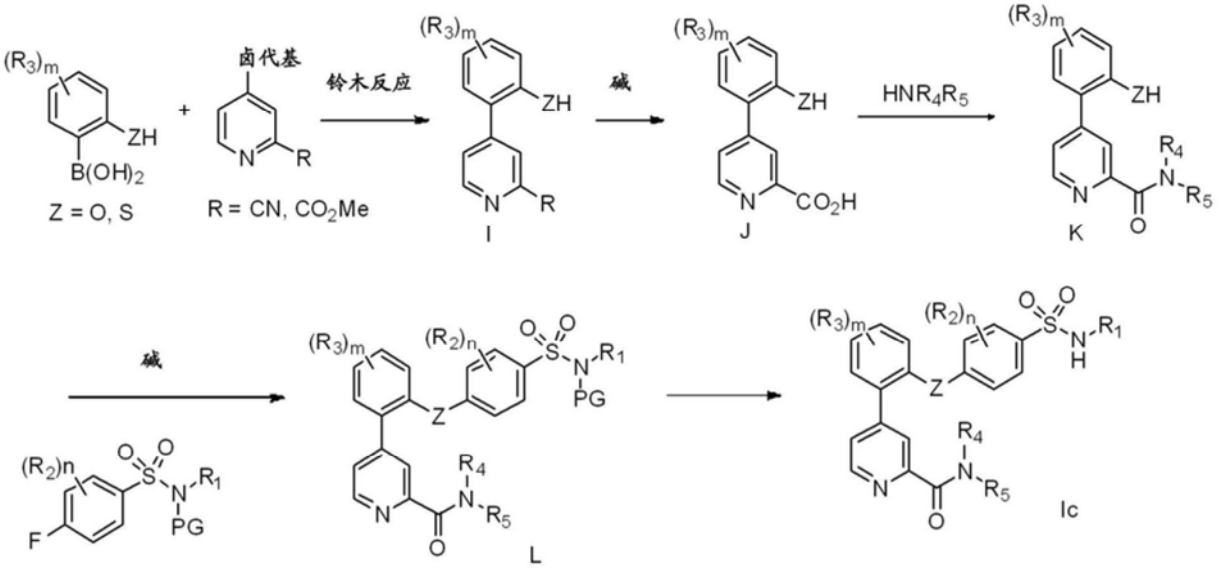
[0351]



[0352] 根据合成方案 3 合成式（Ic）的化合物。在 R_3 取代的 2- 羟基硼酸或 2- 巯基硼酸和吡啶的衍生物（如 4- 卤代 - 氰基吡啶或 4- 卤代 - 吡啶酯（例如，甲基吡啶））之间的铃木偶联反应提供中间产物 I，其中卤取代基是氯或溴取代基。中间产物 I 与碱（如氢氧化钾）反应以得到中间产物 J。中间产物 J 通过使用例如 EDC 和 HOBt 与 NHR_4R_5 反应以形成酰胺中间产物 K。中间产物 K 在存在碱（如碳酸钾）的情况下与氟代苯基磺酰胺反应，以得到中间产物 L，其中磺酰胺氮可选地由基团，例如 BOC 或 2,4- 二甲氧基苄基保护。中间产物 L 的磺酰胺基团通过使用例如盐酸去保护以得到式（Ic）的化合物。

[0353] 方案 3

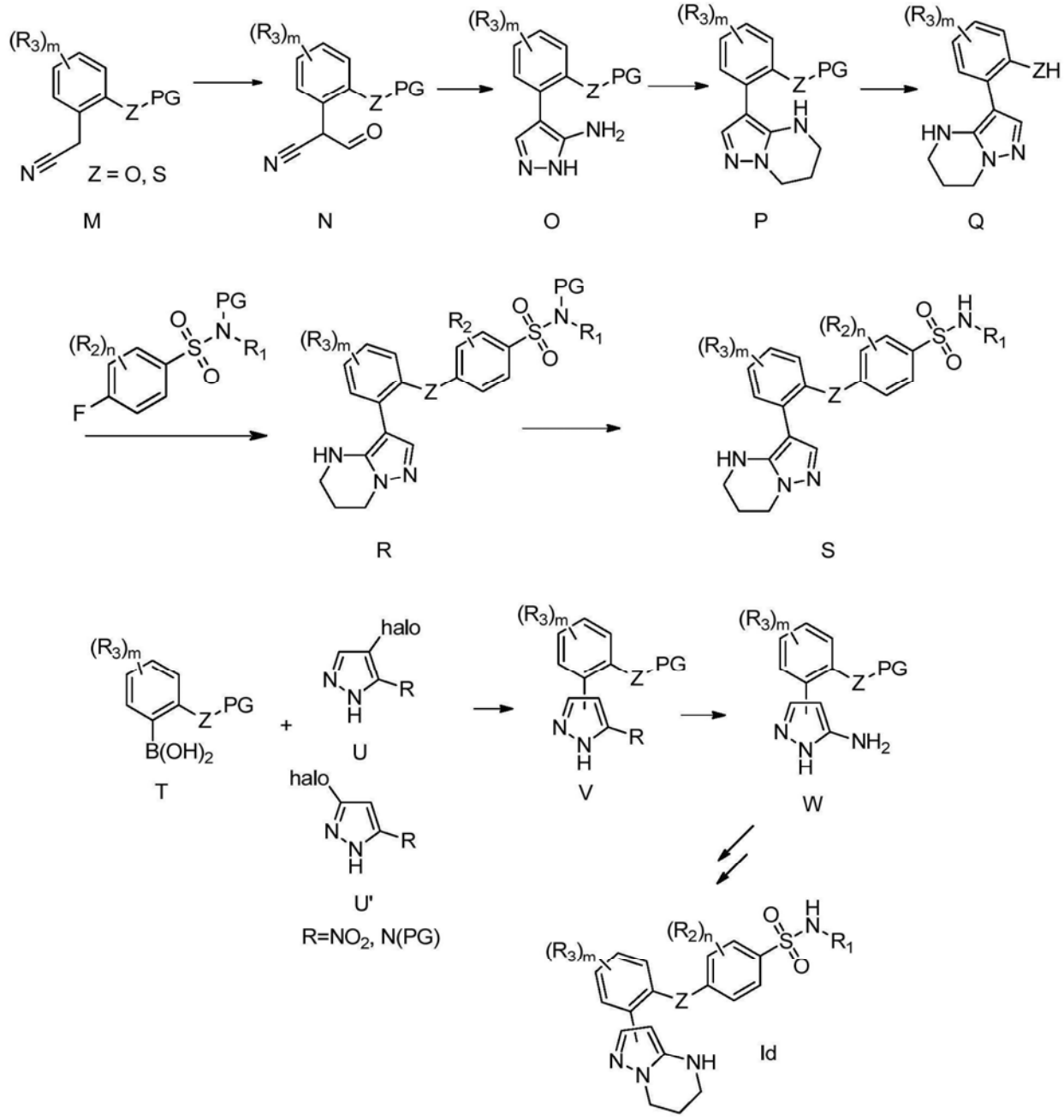
[0354]



[0355] 根据合成方案 4 合成式 (Id) 的化合物。具有受保护的羟基或巯基基团 (例如甲基保护的羟基,即 -OMe 基团) 的苯乙腈的衍生物 M 通过使用例如 Na/ 甲酸乙酯或 NaOEt/ 甲酸乙酯进行甲酰化以得到中间产物 N。中间产物 N 与肼反应以提供中间产物 O。中间产物 O 在碱性条件下,例如,在存在 NaH 或 Cs_2CO_3条件下,与二卤烷烃,例如,1,3- 二溴丙烷,反应以得到中间产物 P。在苯酚或硫醇的去保护之后,例如通过甲基受保护的羟基基团与 BBr_3反应,中间产物 P 可以进行如方案 1、方案 2 或方案 3 所描述的合成顺序以得到化合物 S,即式 (Id) 的化合物。此外,去保护并且经历本段中描述且提及的过程以得到式 (Id) 的化合物的中间产物 W 可以按照如下方式获得 :中间产物 T 在存在碱和钯催化剂的铃木条件下与中间产物 U 或“U”反应得到中间产物 V,其中,中间产物 U 或“U”的 R 是硝基基团或适当保护的氨基基团。中间产物 V 经过以下条件以得到中间产物 W,所述条件使硝基基团还原成氨基基团或去保护氮以释放氨基基团,如乙酸中的锌或氢和阮内镍。

[0356] 方案 4

[0357]



[0358] 4.4 使用方法

[0359] 本文提供了用于治疗或预防有此需要的受试者的疼痛的方法，其中该方法包括将本文中提供的化合物（即，式（I）的化合物、式（Ia）的化合物、式（Ib）的化合物、式（Ic）的化合物、式（Id）的化合物、列于表 1 中的化合物或列于表 2 中的化合物）给药于对这种治疗或预防有需要的患者。

[0360] 本文提供了用于管理疼痛的方法，所述方法包括将治疗有效量的化合物或治疗有效量的盐或其溶剂化物或互变异构形式给药于有此需要的受试者。

[0361] 本文提供了用于治疗神经性疼痛的方法，所述方法包括将治疗有效量的化合物或治疗有效量的盐或其溶剂化物或互变异构形式给药于有此需要的受试者。

[0362] 本文提供了用于治疗疼痛的方法，所述方法包括使用化合物作为电压依赖性钠通道抑制剂。在具体实施方式中，这些方法是其中的疼痛为神经性疼痛、伤害性疼痛或炎性疼

痛的方法。在具体实施方式中，这些方法是其中的电压依赖性钠通道为 NaV1.7 的方法。

[0363] 本文提供了用于治疗或预防 NaV1.7 功能障碍有关的障碍的方法，所述方法包括将治疗有效量的化合物或治疗有效量的盐或其溶剂化物或互变异构形式给药于有此需要的受试者。

[0364] 本文提供了用于预防或治疗受试者中的疼痛的方法，其中所述方法包括将治疗有效量的化合物给药于需要这种预防或治疗的受试者。在具体实施方式中，所述方法是其中的治疗有效量的化合物对减轻受试者中的疼痛有效的方法，其中所述化合物以 0.1mg/kg 至 1,000mg/kg 的剂量、以 0.5mg/kg 至 100mg/kg 的剂量、以 1mg/kg 至 50mg/kg 的剂量或 5mg/kg 的剂量在福尔马林试验（在阶段 1 或阶段 2，或两个阶段中）（参见 5.1.2 小节）表现出减小疼痛反应。在某些实施方式中，本文提供的化合物表现出在福尔马林试验（在阶段 1 或阶段 2，或两个阶段中）中比空白对照减少至少 10％、20％、30％、40％、50％、60％、70％、80％、90％、95％、98％、99％、或 100％，或在任意的列举的百分比范围之间（例如，10-20％、10-30％、10-40％、20-30％、或 20-40％）的范围内的疼痛反应。在具体实施方式中，所述方法是疼痛为以下各项的方法：伤害性疼痛，如由物理创伤导致的疼痛（例如，皮肤的切口或挫伤；或化学烧伤或热烧伤）、骨关节炎、类风湿性关节炎或肌腱炎；肌筋膜疼痛；神经性疼痛，如与如与中风、糖尿病性神经病、梅毒性神经病、带状疱疹后神经痛、三叉神经痛、纤维肌痛、或由药物医源性地诱导的疼痛性神经病相关的神经性疼痛；或混合型疼痛（即，具有伤害性和神经性成分的疼痛）；内脏疼痛；头痛（例如，偏头痛）；CRPS；CRPS I 型；CRPS II 型；RSD；反射性神经血管营养不良；反射性营养不良；交感神经维持疼痛综合征；灼痛；祖德克骨萎缩；痛觉神经营养不良；肩手综合征；创伤后营养不良；自主机能障碍；自身免疫相关的疼痛；炎症相关的疼痛；癌症相关的疼痛；幻肢痛；慢性疲劳综合征；手术后的疼痛；脊髓损伤性疼痛；卒中后中枢痛；神经根病；对皮肤的温度、轻触或颜色变化的敏感性（痛觉超敏）；源于高热或低热病症的疼痛；和其它疼痛病症（例如，糖尿病性神经病、梅毒性神经病、带状疱疹后神经痛、三叉神经痛）；慢性疼痛；或急性疼痛。

[0365] 本文提供了调控电压依赖性钠通道的活性的方法，其中所述方法包括使表达电压依赖性钠通道的细胞与化合物接触。在具体实施方式中，所述方法是其中的电压依赖性钠通道为 NaV1.7 的方法。在具体实施方式中，所述方法是导致抑制电压依赖性钠通道的方法。

[0366] 在某些实施方式中，本文提供的化合物给药于在编码电压依赖性钠离子通道（例如，NaV1.7）的 α 亚单元基因中具有获得功能突变的患者人群。

[0367] 在某些实施方式中，本文提供的化合物给药于被诊断为红斑性肢痛症、原发性红斑性肢痛症、阵发性极度疼痛障碍 (PEPD) 或 NaV1.7 相关的纤维肌痛的患者人群。

[0368] 4.5 药物组合物和给药途径

[0369] 本文提供了药物组合物，该药物组合物包括本文提供的化合物和可药用的载体。在具体实施方式中，药物组合物是所述化合物适用于局部给药、口服给药、皮下注射给药或静脉给药的药物组合物。

[0370] 本文提供了包括有效量的化合物的组合物，以及包括有效量的化合物和可药用的载体或媒介物的组合物。在一些实施方式中，本文所述的药物组合物适用于口服给药、肠胃外给药、粘膜给药、经皮给药或局部给药。

[0371] 所述化合物可以以常规制备形式，例如，胶囊、微胶囊、片剂、颗粒剂、散剂、糖锭、药丸、栓剂、注射剂、混悬剂和糖浆剂，以口服或肠道外给药方式给药于患者。合适的制剂可以通过使用常规的有机或无机添加剂通常采用的方法来制备，例如赋形剂（例如，蔗糖、淀粉、甘露糖醇、山梨醇、乳糖、葡萄糖、纤维素、滑石、磷酸钙或碳酸钙），粘结剂（例如，纤维素、甲基纤维素、羟甲基纤维素、聚丙基吡咯烷酮、聚乙烯基吡咯烷酮、明胶、阿拉伯树胶、聚乙二醇、蔗糖或淀粉），崩解剂（例如，淀粉、羧甲基纤维素、羟丙基淀粉、低取代羟丙基纤维素、碳酸氢钠、磷酸钙或柠檬酸钙），润滑剂（例如，硬脂酸镁，轻质无水硅酸，滑石粉或月桂基硫酸钠）、调味剂（例如，柠檬酸、薄荷醇、甘氨酸或桔粉），防腐剂（例如，苯甲酸钠、亚硫酸氢钠、对羟基苯甲酸甲酯或对羟基苯甲酸丙酯），稳定剂（例如，柠檬酸，柠檬酸钠或乙酸），悬浮剂（例如，甲基纤维素、聚乙烯吡咯烷酮或硬脂酸铝），分散剂（例如，羟丙基甲基纤维素），稀释剂（例如，水），和底蜡（例如，椰子油、白凡士林或聚乙二醇）。药物组合物中化合物的有效量可以是实现所需效果的水平，例如，对于口服和非肠道给药，约 0.1mg/kg 患者体重至约 1000mg/kg 患者体重或约 0.5mg/kg 患者体重至约 100mg/kg 患者体重的单位剂量。

[0372] 将给药于患者的化合物的剂量可相当宽泛地变化，并且可以由卫生保健从业者来判断。一般而言，所述化合物可以以约 0.1mg/kg 患者体重至约 1000mg/kg 患者体重的剂量每天 1-4 次给药于患者，但是上述剂量可以根据患者的年龄、体重和医疗状况以及给药类型适当地变化。在一个实施方式中，所述剂量是约 0.05mg/kg 患者体重至约 500mg/kg 患者体重、0.05mg/kg 患者体重至约 100mg/kg 患者体重、约 0.5mg/kg 患者体重至约 100mg/kg 患者体重、约 0.1mg/kg 患者体重约至约 50mg/kg 患者体重、或者约 0.1mg/kg 患者体重至约 25mg/kg 患者体重。在一个实施方式中，每天给定一份剂量。在另一个实施方式中，每天给定两份剂量。在任何给定情况下，给药的化合物的量将取决于诸如活性组分的溶解度、使用的剂型和给药途径等因素。

[0373] 在另一个实施方式中，本文提供了用于治疗疼痛的方法，所述方法包括将约 7.5mg/ 天至约 75g/ 天、约 3.75mg/ 天至约 37.5g/ 天、约 3.75mg/ 天至约 7.5g/ 天、约 37.5mg/ 天至约 7.5g/ 天、约 7.5mg/ 天至约 3.75g/ 天、约 3.75mg/ 天至约 1.875g/ 天、约 3.75mg/ 天至约 1,000mg/ 天、约 3.75mg/ 天至约 800mg/ 天、约 3.75mg/ 天至约 500mg/ 天、约 3.75mg/ 天至约 300mg/ 天、或约 3.75mg/ 天至约 150mg/ 天的化合物给药于有此需要的患者。在具体实施方式中，本文公开的方法包括将 1mg/ 天、5mg/ 天、10mg/ 天、15mg/ 天、20mg/ 天、30mg/ 天、40mg/ 天、45mg/ 天、50mg/ 天、60mg/ 天、75mg/ 天、100mg/ 天、125mg/ 天、150mg/ 天、200mg/ 天、250mg/ 天、300mg/ 天、400mg/ 天、600mg/ 天、800mg/ 天、1,000mg/ 天、1,500mg/ 天、2,000mg/ 天、2,500mg/ 天、5,000mg/ 天、或 7,500mg/ 天的化合物给药于有此需要的患者。

[0374] 在另一个实施方式中，本文提供了单位剂量剂型，所述单位剂量剂型包括约 7.5mg 至约 75g、约 3.75mg 至约 37.5g、约 3.75mg 至约 7.5g、约 37.5mg 至约 7.5g、约 7.5mg 至约 3.75g、约 3.75mg 至约 1.875g、约 3.75mg 至约 1,000mg、约 3.75mg 至约 800mg、约 3.75mg 至约 500mg、约 3.75mg 至约 300mg、或约 3.75mg 至约 150mg 的化合物。

[0375] 在具体实施方式中，本文提供了单位剂量剂型，所述单位剂量剂型包括约 1mg、5mg、10mg、15mg、20mg、30mg、40mg、45mg、50mg、60mg、75mg、100mg、125mg、150mg、200mg、

250mg、300mg、400mg、600mg、800mg、1,000mg、1,500mg、2,000mg、2,500mg、5,000mg、 或7,500mg 的化合物。

[0376] 在另一个实施方式中，本文提供了单位剂量剂型，所述单位剂量剂型包括在患者或动物模型中达到化合物的目标血浆浓度的化合物剂量。在具体实施方式中，本文提供了单位剂量剂型，所述单位剂量剂型在患者或动物模型中达到大约 0.001μg/mL 至大约 100mg/mL、大约 0.01μg/mL 至大约 100mg/mL、大约 0.01μg/mL 至大约 10mg/mL、大约 0.1μg/mL 至大约 10mg/mL、大约 0.1μg/mL 至大约 500μg/mL、大约 0.1μg/mL 至大约 500μg/mL、大约 0.1μg/mL 至大约 100μg/mL 或大约 0.5μg/mL 至大约 10μg/mL 的化合物的血浆浓度。为了达到这种血浆浓度，化合物或其药物组合物可以根据给药途径以 0.001μg 至 100,000mg 范围内的剂量给药。在某些实施方式中，后续的化合物的剂量可以根据用给药于受试者的初始剂量的化合物或其药物组合物获得的化合物的血浆浓度相应地进行调节。

[0377] 化合物可以每天给药一次、两次、三次、四次或更多次。

[0378] 出于方便的原因，化合物可以口服给药。在一个实施方式中，当口服给药时，化合物与膳食和水一起给药。在另一个实施方式中，所述化合物分散在水或果汁（例如，苹果汁或橙汁）中并且作为混悬剂口服给药。在另一个实施方式中，当口服给药时，化合物在禁食状态下给药。

[0379] 所述化合物也可以皮内给药；肌内给药；腹膜内给药；皮内给药(intradermally)；静脉内给药；皮下给药；鼻内给药；硬膜外给药；舌下给药；脑内给药；阴道内给药；经皮给药(transdeermally)；直肠给药；粘膜给药；吸入给药；或局部给药于耳、鼻、眼或皮肤。给药方式由卫生保健从业者自由裁量，并且可以部分地取决于医疗状况的位点。

[0380] 在一个实施方式中，本文提供了包含化合物而没有额外的载体、赋形剂或媒介物的胶囊。

[0381] 在另一个实施方式中，本文提供了包括有效量的化合物和可药用的载体或媒介物的组合物，其中可药用的载体或媒介物可以包括赋形剂、稀释剂或其混合。在一个实施方式中，所述组合物是药物组合物。

[0382] 所述组合物可以是片剂、咀嚼片、胶囊、溶液剂、肠外溶液剂、糖锭、栓剂和混悬剂等。组合物可以配制成容纳剂量单位的日剂量，或者日剂量方便的部分，其可以是单个片剂或胶囊或液体的方便体积。在一个实施方式中，所述溶液从水溶性盐制备。一般而言，根据药物化学中熟知的方法来制备所有组合物。通过使化合物与合适的载体或稀释剂混合并且将正确量的混合物填充在胶囊中可以制备胶囊。常用的载体和稀释剂包括，但不限于惰性粉末物质如许多不同种类的淀粉、粉状纤维素，尤其是结晶和微晶纤维素；糖如果糖、甘露糖醇和蔗糖；谷物面粉和类似的可食粉末。

[0383] 可以通过直接压制、湿法造粒或干法造粒来制备。它们的剂型通常掺入稀释剂、粘结剂、润滑剂和崩解剂以及化合物。典型的稀释剂包括，例如，各种类型的淀粉、乳糖、甘露糖醇、高岭土、磷酸钙或硫酸钙；无机盐，例如，氯化钠和糖粉。粉状纤维素衍生物也是可用的。在一个实施方式中，所述药物组合物不含乳糖。典型的片剂粘结剂是例如淀粉；明胶和糖如乳糖、果糖、葡萄糖等物质。天然树胶和合成树胶也是适当的，包括阿拉伯树胶、海藻酸

盐、甲基纤维素、聚乙烯吡咯烷酮等。聚乙二醇、乙基纤维素和蜡类也可以用作粘结剂。

[0384] 在片剂剂型中可能需要润滑剂以防止片剂和冲孔(pouch)粘在芯(die)上。润滑剂可以选自光滑的固体,例如滑石、硬脂酸镁和硬脂酸钙、硬脂酸和氢化植物油。片剂崩解剂是在润湿时溶胀以破碎片剂并释放化合物的物质。它们包括淀粉、粘土、纤维素、褐藻胶和树胶。更具体地讲,可以使用了玉米淀粉和马铃薯淀粉、甲基纤维素、琼脂、膨润土、木纤维素、粉状天然海绵、阳离子交换树脂、藻酸、瓜尔胶、柑橘果肉和羧甲基纤维素,以及月桂基硫酸钠。片剂可以涂有糖作为风味剂和密封剂,或者涂有成膜保护剂以改变片剂的溶解性能。例如,通过在剂型中使用例如甘露糖醇的物质,所述组合物也可以配制成咀嚼片。

[0385] 当希望将化合物作为栓剂给药时,可以使用常用的基料。椰子油是传统的栓剂基料,可以通过添加喇类以稍微提高其熔点来改性。广泛使用水混溶性栓剂基料,特别是包括各种分子量的聚乙二醇。

[0386] 所述化合物的效果可以通过正确的配方来迟释或延长。例如,所述化合物的可缓溶粒料可以制备并掺入片剂或胶囊中,或者作为缓释的可植入的装置。这些技术还包括制备几种不同溶解速率的粒料并且用粒料的混合物填充的胶囊。片剂、胶囊或粒料可以涂有在在可预期的时间段内防止溶解的膜(涂层可以包括,例如,聚甲基丙烯酸酯或乙基纤维素)。通过使所述化合物溶解或悬浮在允许化合物缓慢分散到血清中的油性或乳状媒介物中,甚至可以使肠道制剂变得长效。

[0387] 5 实施例

[0388] 5.1 生物实例

[0389] 5.1.1 体外试验

[0390] 重组 NaV 细胞系

[0391] 在重组细胞系中进行体外试验,该重组细胞系从编码 α 亚单元(hNav1.7,SCN9A)、β 亚单元(SCNB1)和 β 亚单元(SCNB2)的引入的核酸稳定地表达感兴趣的异三聚体蛋白。该细胞系在人类胚胎肾 293 细胞中构建。在体外试验中也可以使用单独地或结合各种 β 亚单元稳定表达重组的 Nav1.7 或 Nav1.5α 亚单元的附加的细胞系。

[0392] 为了制备本文提供的细胞和细胞系,可以使用例如美国专利 6,692,965 和 WO/2005/079462 中描述的技术。这两篇文献通过引用全部引入本文。此技术提供了实时评估数百万个细胞,使得可以选择表达所需的基因的任意所需数量的克隆(从数百至数千克隆)。使用细胞分选技术,例如流式细胞仪细胞分选(例如,使用 FACS 机器)或磁性细胞分选(例如,使用 MACS 机器),在培养皿(例如,96 孔培养板)中以高统计置信度自动沉积每个孔一个细胞。此技术的速度和自动化允许容易分离多基因重组细胞系。

[0393] FDSS 膜电位体外试验

[0394] 膜电位染料(s):与荧光淬灭剂结合的蓝色膜电位染料(Molecular Devices Inc.)、或膜电位敏感染料、HLB021-152(AnaSpec),例如,二苦胺(DPA)、酸性紫 17(AV 17)、二嗪黑(DB)、HLB30818、FD 和 C Black Shade、台盼蓝(Trypan Blue)、溴酚蓝、HLB30701、HLB30702、HLB30703、硝嗪黄、硝基红、DABCYL(分子探针)、FD 和 C Red NO.40、QSY(分子探针)、金属离子淬灭剂(例如,Co^{2+}、Ni^{2+}、Cu^{2+})和碘离子。

[0395] 试验激动剂:藜芦碱和蝎毒蛋白通过重组机制调节电压依赖性钠通道的活性,包括灭活动力学的改变。

[0396] 在稳定的NaV1.7表达细胞中的钠通道的所得的活性改变细胞膜电位并且荧光信号由于去极化而增大。

[0397] 可以从Sigma-Aldrich(St.Louis,MO)购买来自以色列金蝎的藜芦碱和蝎毒。原液在DMSO中制备成10mM(藜芦碱)并且在去离子水中制备成1mg/ml(蝎毒)。钠通道激动剂在试验缓冲剂中稀释成4倍浓度,最终浓度为藜芦碱2-25μM以及蝎毒2-20μg/ml。

[0398] 在DMSO中测试化合物制备成2-10mM原液。原液在DMSO中以连续稀释步骤进一步稀释,然后转移到试验缓冲剂作为最终试验浓度的4倍。在动能读取的第一添加(预刺激)步骤期间添加测试化合物。所有的测试化合物浓度以一式三份进行评估。

[0399] 稳定表达NaV1.7α、β1和β2亚单元的细胞在用10%胎牛血清、谷氨酰胺和HEPES补充的Dulbecco's Modified Eagles培养基中维持在标准细胞培养条件下。在试验的前一天,使用细胞分离剂,例如胰蛋白酶、CDB(GIBCO)或细胞剥离剂(Mediatech),从原液板收获细胞,并且在生长培养基中在384孔培养板上以每孔10000-25000个细胞装板。试验板在5% CO_2的条件下在37℃的细胞培养箱中维持22-48小时。然后从试验板去除培养基,并且添加在上样缓冲液(137mM NaCl、5mM KCl、1.25mM $CaCl_2$、25mM HEPES、10mM葡萄糖)中稀释的膜电位荧光染料。细胞与膜电位染料一起在37℃温育45-60分钟。然后将染料上样试验板放置在高通量荧光板读数器(Hamamatsu FDSS)中。动能读数开始每秒对试验板成像。在10秒后,试验缓冲液单独、或者试验缓冲液中稀释的测试化合物添加到细胞(第一添加步骤)中,并且动能读数继续,每2秒一次,总共2分钟,此后用在试验缓冲液中稀释的藜芦碱和蝎毒刺激细胞(第二添加步骤)以评估测试化合物的效果。

[0400] 仅具有缓冲液的藜芦碱和蝎毒(未添加测试化合物)引出的对照响应作为最大响应。试验结果以相对荧光单位(RFU)表示并且可以通过在第二添加/刺激步骤期间使用最大信号或者通过在第二添加/刺激步骤期间计算最大和最小信号的差异来确定。针对每种测试化合物浓度以一式三份评估信号抑制。使用GraphPad Prism 5.01软件来分析数据以确定测试化合物的IC50值。

[0401] 实施例1、2、3、12、13、16、26、32表明IC50值小于0.13μM;实施例4、5、6、7、8、9、10、15、18、20和28表明IC50值在0.13至1.0μM之间;实施例14、17、19、21、22和23表明IC50值大于1.0μM和20.0μM。

[0402] Patchliner电生理学体外试验

[0403] 在Patchliner®设备(Nanion Technologies)上记录来自表达NaV1.7或NaV1.5的稳定的HEK293细胞系的钠电流。Patchliner®是全自动台式膜片钳平台并且可以用GΩ密封同时记录高达8个单独的细胞。

[0404] 对于膜片钳实验,细胞用10%胎牛血清、谷氨酰胺和HEPES补充的Dulbecco's Modified Eagles培养基中的标准培养条件下生长。收获细胞,并且将细胞保持在悬浮液中高达4小时,膜片的质量或能力没有明显变化。根据Nanion的Patchliner®的标准程序进行整个细胞膜片钳记录。实验在室温下进行。

[0405] 设计电压方案以建立:1)峰值电流幅值(Imax),2)测试电位(Vmax)和3)8个单独的细胞中的每个的半失活电位。为了确定V1/2,执行标准稳态失活方案,使用一系列15个500ms去极化预脉冲,10mV的增量(在-130mV开始),紧接着是10ms测试脉冲至Vmax。为了评估测试化合物对钠通道(Ki)的灭活状态的亲和力,每个细胞的保持电位自动设置成

从稳态灭活数据计算的V1/2。电流用以下电压方案激活：在V1/2保持2-5s，返回到-120mV持续5-10ms以缓解快速失活，阶跃到测试电位(Vmax)持续10-20ms。此电压方案每10s重复一次，以添加2-3次缓冲液随后添加测试化合物来建立基线。通过使用Nanion数据分析包来分析剂量依赖性抑制。

[0406] 实施例1、2、5、6、8、11、12、13、15、16、20、24、26、28、29和32表明IC50值小于0.1μM；实施例14、17、18、19、21、22、23、25和33表明IC50值在0.1至1.0μM之间。

[0407] 用于测量药物代谢的体外细胞色素P450(CYP450)试验

[0408] 使用根据制造商指导的高通量兼容的基于荧光的CYP450筛选试验(Vivid® CYP450，Invitrogen)来评估药物候选项与细胞色素P450酶的相互作用，该细胞色素经由氧化代谢是药物清除的主要决定因素。简而言之，四种不同浓度(μM-6.0、2.0、0.7、0.2)的测试化合物、正对照(酮康唑)和溶剂对照在具有CYP3A4酶复合物的96孔微量滴定板的唯一孔中在室温下温育20分钟。在温育开始使用Tecan Safire^{2}微板读数器-单色仪测量预读荧光(Ex-485nm/Em-530nm)以确定背景荧光。在温育阶段结束时，添加酶底物和辅酶，并且通过每分钟测量荧光来动能监测反应1小时。测试化合物对提供的底物的CYP3A4代谢的影响通过计算存在测试化合物的有效反应速率与不存在抑制剂的有效反应速率的比值来确定。

[0409] 实施例9、11、13、14、15、17、18、19、21和22表明在6mM测试浓度0-25％的CYP3A4抑制；实例5、6、8、10和16表明在6mM测试浓度25-50％的CYP3A4抑制；实例1、2、3、4、12、20和32表明在6mM测试浓度50-100％的CYP3A4抑制。

[0410] 5.1.2体内试验

[0411] 福尔马林试验的方法

[0412] 福尔马林测试(疼痛行为)产生两阶段反应，1阶段(福尔马林注射后0至10分钟)涉及直接损伤感觉神经末梢的伤害感受器并且模仿术后疼痛和伤口疼痛，而2阶段(福尔马林注射后11至40分钟)涉及模仿炎症性关节炎(关节疼痛)的神经发炎疼痛。

[0413] 每个动物在测试之前适应2-3天。在适应之后，测试化合物、正对照(例如抑制疼痛熟知的美西律或利多卡因)或空白对照(例如，生理盐水)在施用福尔马林之前15-20分钟通过腹腔内注射或管饲法施用。记录施用测试化合物的时间。PBS的福尔马林溶液(1.25％)在时间(T)＝0分钟以50μL的体积皮下注射(s.c)到每只鼠的后爪足背中。然后每个动物放置在透明的观察室中。在注射后T＝1分钟至60分钟开始观察。通过自动伤害感受分析仪记录每个动物每分钟的畏缩(舔、咬或摇晃)次数。这通过测量在施用测试化合物之前15-30分钟放置在注射爪附近的踝关节上的小金属带(0.5g)的运动来实现。福尔马林注射到具有金属带的爪中，然后将动物不受约束地放置在观察室中通过电磁检测系统检测。爪畏缩由系统检测并且使用计算机自动计数。在测试结束时，写出包含每个动物的识别信息以及随时间变化每分钟的畏缩次数。在给药后75分钟进行错步实验。在整个研究期间，记录运动变化，例如，不动和惊厥的其他观察。

[0414] 实施例1、2、6、8和12表明在经由腹膜内注射途径的3-30mg/kg剂量相对于空白对照减少24-78％(福尔马林试验，1阶段)和29-73％(福尔马林试验，2阶段)的疼痛反应。

[0415] 实施例1表明在经由口服途径的75mg/kg剂量相对于空白对照减少14％(福尔马

林试验,1 阶段）和 17％（福尔马林试验,2 阶段）的疼痛反应。

[0416] 实施例 12 表明在经由局部给药途径的 1％或 2％ w/v 的 150μL 剂量相对于空白对照减少 13-24％（福尔马林试验,1 阶段）和 29-43％（福尔马林试验,2 阶段）的疼痛反应。

[0417] 部分坐骨神经结扎 (PSNL) 的方法

[0418] 部分坐骨神经结扎模型与神经性疼痛（例如,脊椎椎间盘膨出和糖尿病神经损伤）相关。

[0419] 来自适当的动物资源的 250-350g 雌性 SD 大鼠 (Sprague-Dawley rats) 用 2.5％异氟烷麻醉。后肢剃毛,皮肤用 0.5％碘和 75％乙醇消毒。所有的手术器械在手术之前并且在动物之间消毒。在与肌肉和坐骨神经分布平行的大腿中间切出切口 (1cm)。使肌肉裸露,并且在浅色（白色）筋膜线表示的两块肌肉（股二头肌）的接头处切开。坐骨神经刚好在肌肉下方,然后使用 18-20G 的喂食针（弯曲 90 度）钩出 ;坐骨神经平放在喂食针上并且用 7-0 缝合丝线紧紧地结扎神经的大约一半直径。受伤的腿抽搐的反应表明结扎成功。在检查止血之后,给切口区域 0.1-0.2ml(0.125％）布比卡因,用 5-0 吸收性缝线封闭肌肉和相邻的筋膜。皮肤用可吸收缝合线和组织胶缝合。假手术的动物（约 8-10 只动物）经过相同的手术过程,但是不结扎。动物在从麻醉状态恢复之后返回到它们的养笼中。

[0420] 以下行为测试在第 3 天开始,并且此后一周一次以下手术。

[0421] 热痛觉过敏：

[0422] 脚底测试定量地评估后爪的热阈值。大鼠放置在热测试设备（型号 336, IITC/Life Science Instruments,Woodland Hills,CA) 的玻璃表面上,并且允许在室温下在玻璃表面上测试之前适应 10 分钟。将动物放置在观察室中,玻璃表面的温度恒定地维持在 30-32℃。位于玻璃下方的活动辐射热源聚焦在每只大鼠的后爪上。设备设置在 55％（加热速率～ 3℃ /s) 加热强度,在 10 秒截止。通过数字定时器记录爪缩回潜伏时间。热阈值确定为两只后爪两次或三次连续试验的平均缩回潜伏时间。10 秒截止用于防止潜在的组织损伤。

[0423] 机械痛觉过敏

[0424] 爪压力测试评估伤害感受性机械阈值（以克计),并且用 Ugo Basil Analgesimeter(Varese,Italy) 测量。该测试通过在后肢上施加有害（疼痛的）压力来进行。通过压下启动马达的踏板,力以线性比例增大 (32g/s)。当动物通过缩回爪或发出声音表现疼痛时,立即释放踏板并且在刻度上读取伤害感受性疼痛阈值 (150g 的截止用于避免组织损伤)(Courteix 等,1994)。两只后爪都用于评估机械痛觉过敏。每只大鼠进行至少两次试验,间隔 10 分钟,并且使用平均值。特定大鼠的测试过程在 5 分钟适应之后开始,或者在大鼠一旦停止嗅探并表现出适应测试环境就开始。

[0425] 触觉异常性疼痛

[0426] Von Frey 测试量化后爪的机械敏感性。该测试利用非有害刺激,并且因此被当作测量触觉异常性疼痛。动物放置在金属丝网地面上的透镜塑料盒下,这允许完全与爪接触。允许至少 5 分钟行为适应。机械缩爪阈值 (PWT) 用上下测试范例进行测量。在中跖爪神经性疼痛（即, PSNL) 的动物上施加持续 2-3s 的以对数增加力 (2.0、4.0、6.0、8.0、10.0、15.0、26、60g 或大小为 4.31、4.56、4.74、4.93、5.07、5.18、5.46、5.88) 的 Von Frey 细丝。施加在

跖面的中心区域，避免脚垫。首先施加 4.0g 刺激。每当对给定探针产生退缩反应时，施加下一个更小的 Von Frey 探针。每当产生负响应时，施加下一个更高的 Von Frey 探针。测试持续直到 (1) 在已经获得第一次反应变化之后对多于 4 次刺激的反应（总共 3-5 次试验），或 (2) 达到 Von Frey 纤毛的上 / 下端（弯曲）。如果动物对任何 Von Frey 纤毛没有反应，26g 的值，与下一个以对数增加的潜在的 Von Frey 细丝对应，被指定为阈值。该测试持续直到确定引起快速弹爪的具有最低的力的纤毛，或者当达到大约 26g 截止的力时。使用该截止的力，因为它代表动物体重的大约 10％并且用于防止由于使用更硬的纤毛而抬起整个后肢，这会改变刺激的本质。通过测量纤毛在放置在电子天平上时施加的以克计的大小来每周一次确认每根纤毛的值。仅当大鼠静止并且全部四个爪站立时施加纤毛。仅当后爪从平台完全移开时认为退缩反应有效。尽管少见，但是如果大鼠在施加纤毛之后立即走动而不是仅仅抬起爪，那么重新施加纤毛。在偶然情况下，后爪仅在单次施加之后畏缩，由于未从平台提起后爪，这不被认为是退缩反应。试验包括以 5 秒间隔在后爪上施加 Von Frey 纤毛 5 次，或者一旦后爪适当地放置在平台上就施加 Von Frey 纤毛。如果在 5 次施加特定纤毛期间没有发生退缩，就以类似方式施加这个系列中下一个较大的纤毛。当后爪在 5 次施加的 4 次或 5 次中从特定的纤毛退缩时，以克计的纤毛的值被认为是退缩阈值。一旦确定了左后肢的阈值，在 5 分钟之后对右后肢重复相同的测试过程。

[0427] 承重

[0428] 在称重测试中，使用 Incapacitance tester(Linton Instruments,Norfolk,UK) 测试大鼠的超敏反应和自发性疼痛。大鼠放置在设备的塑料盒中。在此期间 (1-2s)，针对右腿和左腿单独显示一体式爪压力。右腿和左腿的压力的比率被计算作为左 / 右后肢重量分布比。称重试验在 5 分钟内重复 3 次。计算 3 次试验的平均分布比。

[0429] 实施例 1 和 2 表明在经由腹膜内注射途径的 30mg/kg 的剂量相对于空白对照恢复 49-62％（爪压力测试）、59-73％（跖测试）和 50-66％（承重）的疼痛反应。

[0430] 扭体反应模型

[0431] 乙酸扭体反应模型与内脏痛（腹痛，例如胃痛，以及例如由胆管拥塞和肾结石引起的疼痛）相关。

[0432] 扭体反应测试评估急性腹内脏痛。在适应 2-3 天之后，测试化合物、正对照或空白对照在施用乙酸之前 15-30 分钟通过腹膜内注射 (i.p.) 或管饲法施用。记录施用测试化合物的施用时间。对于小鼠 :腹膜内注射 10ml/kg 体积的生理盐水中 0.6％乙酸的溶液。对于大鼠 :在时间 T-0 分钟腹膜内注射 2ml/kg 体积的生理盐水中 4％乙酸的溶液。每个动物放置在透明的塑料笼中。在 T ＝ 5 分钟，在 45 分钟时间段内对扭体反应运动的次数计数。可替代地，扭体反应运动在 5 分钟内进行计数并且每 5 分钟进行重复，在 45 分钟时间段内在 T ＝ 5 分钟时开始。

[0433] 实施例 2 表明在经由腹膜内注射途径的 10-30mg/kg 剂量相对于空白对照减少 48-58％的疼痛反应。

[0434] 5.2 NaV 调节剂的实例

[0435] 5.2.1 一般方法

[0436] 5.2.1.1 LCMS 方法

[0437] 方法 A

[0438] LC-MS 在 Acquity H-Class UPLC、PDA 和 SQ 检测器上进行。使用的离子柱是 BEH C18 50×2.1mm×1.7 微米，并且柱流是 0.55ml/ 分钟。流动相使用 (A)0.1％甲酸 +5mM 醋酸铵的水溶液以及 (B)0.1％甲酸的乙腈溶液。紫外线光谱记录在其 λ 最大值，并且使用 ESI 计数记录质谱。以下梯度用于监测反应进程并且分析最终产物。

[0439]

时间（分钟）	％ A	％ B
0.01	95	05
0.40	95	05
0.80	65	35
1.20	45	55
2.50	00	100
3.30	00	100
3.31	95	05
4.00	95	05

[0440] 方法 B

[0441] LC-MS 在 Waters LC alliance 2995、PDA2996 和 SQ 检测器上进行。使用的离子柱是 X-BRIDGE C18 150×4.6mm×5 微米，并且柱流是 1.0ml/ 分钟。流动相使用 (A)0.1％氨水以及 (B)0.1％铵的乙腈溶液。紫外线光谱记录在其 λ 最大值，并且使用 ESI 计数记录质谱。以下梯度用于监测反应进程并且分析最终产物。

[0442]

时间（分钟）	％ A	％ B
0.01	90	10
5.00	10	90
7.00	00	100
11.00	00	100
11.01	90	10
12.00	90	10

[0443] 方法 C

[0444] LC-MS 在 Waters LC alliance 2995、PDA2996 和 SQ 检测器上进行。使用的离子

柱是 X-BRIDGE C18 150×4.6mm×5 微米，并且柱流是 1.0ml/ 分钟。流动相使用 (A)0.1％氨水以及 (B)0.1％铵的乙腈溶液。紫外线光谱记录在其 λ 最大值，并且使用 ESI 计数记录质谱。以下梯度用于监测反应进程并且分析最终产物。

[0445]

时间（分钟）	％ A	％ B
0.01	100	00
7.00	50	50
9.00	00	100
11.00	00	100
11.01	100	00
12.00	100	00

[0446] 方法 D

[0447] LC-MS 在 Waters LC alliance 2995、PDA2996 和 SQ 检测器上进行。使用的离子柱是 X-BRIDGE C18 150×4.6mm×5 微米，并且柱流是 1.0ml/ 分钟。流动相使用 (A)20mM 醋酸铵的水溶液以及 (B)100％甲醇。紫外线光谱记录在其 λ 最大值，并且使用 ESI 计数记录质谱。以下梯度用于监测反应进程并且分析最终产物。

[0448]

时间（分钟）	％ A	％ B
0.01	90	10
5.00	10	90
7.00	00	100
11.00	00	100
11.01	90	10
12.00	90	10

[0449] 5.2.1.2 HPLC 方法

[0450] 方法 A

[0451] HPLC 在 Waters e2695、PDA 检测器上进行。使用的离子柱是 Phenomenex Gemini，C18 150×4.6mm×5 微米，并且柱流是 1.00ml/ 分钟。流动相使用 (A)0.1％甲酸的水溶液以及 (B)0.1％甲酸的乙腈溶液。紫外线光谱记录在其 λ 最大值。使用以下梯度。

[0452]

时间（分钟）	% A	% B
0.01	90	10
7.00	10	90
9.00	00	100
13.00	00	100
13.01	90	10
17.00	90	10

[0453] 方法 B

[0454] HPLC 在 Waters e2695、PDA 检测器上进行。使用的离子柱是 Phenomenex Gemini，C18 150×4.6mm×5 微米，并且柱流是 1.00ml/ 分钟。流动相使用 (A)0.1％甲酸的水溶液以及 (B)0.1％甲酸的乙腈溶液。紫外线光谱记录在其 λ 最大值。使用以下梯度。

[0455]

时间（分钟）	% A	% B
0.01	100	00
7.00	50	50
9.00	00	100
13.00	00	100
13.01	100	00
17.00	100	00

[0456] 方法 C

[0457] HPLC 在 Waters e2695、PDA 检测器上进行。使用的离子柱是 X-BRIDGE，C18 150×4.6mm×5 微米，并且柱流是 1.00ml/ 分钟。流动相使用 (A)0.1％氨水以及 (B)0.1％铵的乙腈溶液。紫外线光谱记录在其 λ 最大值。使用以下梯度。

[0458]

时间（分钟）	% A	% B
0.01	90	10
7.00	10	90
9.00	00	100

13.00	00	100
13.01	90	10
17.00	90	10

[0459] 方法 D

[0460] HPLC 在 Waters e2695、PDA 检测器上进行。使用的离子柱是 X-BRIDGE，C18 150×4.6mm×5 微米，并且柱流是 1.00ml/ 分钟。流动相使用 (A)0.1％氨水溶液以及 (B)0.1％铵的乙腈溶液。紫外线光谱记录在其 λ 最大值。使用以下梯度。

[0461]

时间（分钟）	％ A	％ B
0.01	100	00
7.00	50	50
9.00	00	100
13.00	00	100
13.01	100	00
17.00	100	00

[0462] 5.2.1.3 PREP HPLC 方法

[0463] 方法 A

[0464] PREP HPLC 在 Shimadzu UFLC、LC-20AP 和 UV 检测器上进行。离子柱使用 Sunfire OBD，C_18 250×19mm×5 微米，并且柱流是 18.00ml/ 分钟。流动相使用 (A)0.1％ HCL 的水溶液以及 (B)100％乙腈。紫外线光谱记录在其 λ 最大值。使用以下梯度。

[0465]

时间（分钟）	％ A	％ B
0.01	90	10
7.00	10	90
9.00	00	100
13.00	00	100
13.01	90	10
17.00	90	10

[0466] 方法 B

[0467] PREP HPLC 在 Shimadzu UFLC、LC-20AP 和 UV 检测器上进行。离子柱使用 Sunfire OBD，C18 250×19mm×5 微米，并且柱流是 18.00ml/ 分钟。流动相使用 (A)0.1％甲酸的水溶液以及 (B)0.1％甲酸的乙腈溶液。紫外线光谱记录在其 λ 最大值。使用以下梯度。

[0468]

时间（分钟）	％ A	％ B
0.01	90	10
7.00	10	90
9.00	00	100
13.00	00	100
13.01	90	10
17.00	90	10

[0469] 方法 C

[0470] PREP HPLC 在 Shimadzu UFLC、LC-20AP 和 UV 检测器上进行。使用的离子柱是 X-BRIDGE，C18 250×19mm×5 微米，并且柱流是 18.00ml/ 分钟。流动相使用 (A)0.1％氨水以及 (B)0.1％铵的乙腈溶液。紫外线光谱记录在其 λ 最大值。使用以下梯度。

[0471]

时间（分钟）	％ A	％ B
0.01	90	10
7.00	10	90
9.00	00	100
13.00	00	100
13.01	90	10
17.00	90	10

[0472] 5.2.1.4 缩写列表

[0473] Ac ＝乙酰基

[0474] EtOAc ＝乙酸乙酯

[0475] Bn ＝苄基

[0476] Boc ＝叔丁氧羰基

[0477] Bzl ＝苄基

[0478] DBU = 1,8- 二氮杂二环 [5.4.0] 十一碳 -7- 烯

[0479] DCC = 1,3- 二环己基碳二亚胺

[0480] DCM = 二氯甲烷

[0481] DEAD = 偶氮二甲酸二乙酯

[0482] DIC = 二异丙基碳二亚胺

[0483] DIPEA = 二异丙基乙胺

[0484] D.M.water = 软化水

[0485] DME = 1,2- 乙二醇二甲醚

[0486] DMF = N,N- 二甲基甲酰胺

[0487] DMSO = 二甲基亚砜

[0488] EDC = 1- 乙基 -3-(3- 二甲氨基丙基) 乙基碳二亚胺盐酸盐

[0489] Et2O = 乙醚

[0490] HOBt = 1- 羟基苯并三唑

[0491] IPA = 异丙醇

[0492] KHMDS = 双 (三甲基硅基) 氨基钾

[0493] LAH = 氢化铝锂

[0494] LDA = 二异丙基氨基锂

[0495] LHMDS = 双 (三甲硅基) 氨基锂

[0496] MOM = 甲氧基甲基

[0497] NaHMDS = 双 (三甲硅基) 氨基钠

[0498] NBS = N- 溴代琥珀酰亚胺

[0499] Ph = 苯基

[0500] PMB = 对甲氧基苄基

[0501] Py = 吡啶

[0502] TEA = 三乙基胺

[0503] TFA = 三氟乙酸

[0504] THF = 四氢呋喃

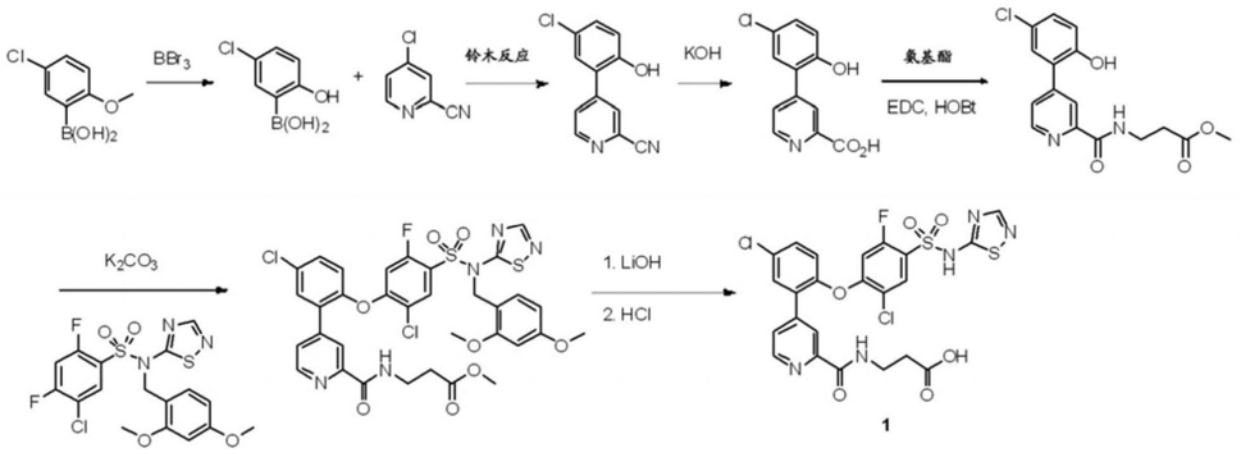
[0505] Tol = 对 - 甲苯酰基

[0506] 5.2.2 实施例

[0507] 实施例 1 :合成 3-(4-(2-(4-(N-1,2,4- 噻二唑 -5- 基氨磺酰基)-2- 氯 -5- 氟苯氧基)-5- 氯苯基) 甲基吡啶酰氨基) 丙酸

[0508] 方案 5

[0509]



[0510] 步骤 1：制备 (5- 氯 -2- 羟苯基) 硼酸。

[0511] 二氯甲烷 (100ml) 中 5- 氯 -2- 甲氧基苯基硼酸 (10.0g,53.6mmol) 冷却至 5-10℃之间的温度。使用均压滴液漏斗在 30 分钟的时间段在上述混合物中内逐滴添加 DCM 中三溴化硼的 100ml 1M 溶液。所得反应混合物在室温下搅拌 30 分钟。在完成反应之后，将该混合物逐滴倒入冰冷的饱和的碳酸氢钠溶液 (600ml) 中。允许在室温下搅拌所得混合物 1 小时。分离出 DCM 层，并且由此收集的水性层冷却至 10-15℃之间的温度。然后将稀释盐酸的 1N 溶液添加到上述冷却的水性层，并且得到沉淀形成物。固体在真空下滤出并干燥以提供 9g(产率 97％) 产物。LC-MS :m/z = 170.9(M+H)。

[0512] 步骤 2：制备 4-(5- 氯 -2- 羟基苯基) 甲基吡啶腈

[0513] 在室温下依次添加 (5- 氯 -2- 羟基苯基) 硼酸 (1.49g,8.65mmol) 和碳酸钾 (3.99g,21.64mmol) 到 4- 氯甲基吡啶腈 (1.0g,7.2mmol) 在 IPA :甲苯 (7ml :7ml) 的溶液中。所得的反应混合物通过用氮气吹扫 15 分钟来除气。此后计算量的 Tetrakis(0.416g, 0.36mmol) 添加到反应混合物中，氮气吹扫进一步持续下一个 20 分钟。所得的反应混合物然后在 100℃回流 20 小时。在完成反应之后，在真空下浓缩混合物。在所得的粗块中加水 (50ml)，然后用乙酸乙酯 (3×25ml) 提取混合物。结合的有机提取物用水 (20ml)、盐水 (20ml) 冲洗，通过硫酸钠干燥，并且在真空下浓缩以获得所需的粗产物。使用正相硅胶通过柱层析纯化粗产物。所需的产物在大约 20-30％乙酸乙酯的己烷中洗脱。产物馏分蒸发得到固态的 0.8g(产率 48％) 所需的产物。LC-MS :m/z = 231.1(M+H)。

[0514] 步骤 3：制备 4-(5- 氯 -2- 羟基苯基) 吡啶甲酸)

[0515] 在 4-(5- 氯 -2- 羟苯基) 甲基吡啶腈 (0.5g,2.17mmol) 的 THF(20ml) 的溶液中添加氢氧化钾 (4.276g,14mmol) 的水 (10ml) 的溶液。所得反应混合物然后在 100℃回流 5 小时。在完成反应之后，在真空下浓缩该混合物。将冰冷的水添加到反应混合物中，然后用 1N HCl 酸化所得的混合物至 pH 3-6。过滤并干燥所得的固体沉淀物以提供固态的 0.5g(产率 93％) 的产物。LC-MS :m/z = 249.8(M+H)。

[0516] 步骤 4：制备甲基 -3-(4-(5- 氯 -2- 羟基苯基)- 吡啶甲基酰胺基) 丙酸酯)

[0517] 在 0℃下，在 4-(5- 氯 -2- 羟苯基) 吡啶甲酸 (0.6g,2.40mmol) 的 THF(20ml) 中依次添加 EDC(0.69g,3.61mmol) 和 HOBT(0.49g,3.61mmol)。反应混合物在 0℃搅拌 30 分钟。在 0℃下，添加 β- 丙氨酸甲酯 (0.40g,2.88mol)。然后允许反应混合物的温度升高到室温，并且搅拌 20 小时。在完成反应之后，将水 (50ml) 添加到反应混合物中。然后用乙酸

乙酯（3×25ml）提取所得的混合物。结合的有机提取物用水（20ml）、盐水（20ml）冲洗，通过硫酸钠干燥，并且在真空下浓缩以获得所需的粗产物。使用正相硅胶通过柱层析纯化粗产物。所需的产物在大约 0-5％甲醇的二氯甲烷中洗脱。产物馏分蒸发得到 0.72g（产率 89％）所需的产物。LC-MS :m/z ＝ 335.6(M+H)。

[0518] 步骤 5：合成甲基 -3-(4-(5- 氯 -2-(2- 氯 -4-(N-(2,4- 二甲氧基苄基）-N-(1,2,4- 噻二唑 -5- 基）氨磺酰）-5 氟苯氧基）苯基）吡啶酰胺基）丙酸甲酯）

[0519] 在氮气气氛的室温下，在甲基 -3-(4-(5- 氯 -2- 羟基苯基）吡啶酰胺基）丙酸酯）(0.72g,2.15mmol) 的 DMF(10ml) 的溶液中添加一份 K_2CO_3(0.59g,4.3mol)。所得反应混合物允许在室温下搅拌 15 分钟。然后上述反应混合物添加计算量的 5- 氯 -N-(2,4- 二甲氧基）-2,4- 二氟 -N-(1,2,4- 噻二唑 -5- 基）苯磺酰胺 (1.0g,2.15mol)。所得反应混合物进一步允许在室温下搅拌 3 小时。在完成反应之后，添加水 (10ml)，然后用乙酸乙酯 (3×25ml) 提取混合物。结合的有机提取物用水 (20ml)、盐水 (20ml) 冲洗，通过硫酸钠干燥，并且在真空下浓缩。粗产物通过使用正相硅胶的柱层析来纯化。所需的产物在大约 20-25％乙酸乙酯的己烷中洗脱。产物馏分蒸发得到 1.0g（产率 60％）所需的产物。LC-MS :m/z ＝ 776.3(M+H)。

[0520] 步骤 6：制备 3-(4-(5- 氯 -2-(2- 氯 -4-(N-(2,4- 二甲氧基苄基）-N-(1,2,4- 噻二唑 -5- 基）氨磺酰）-5- 氟苯氧基）苯基）吡啶酰胺基）丙酸）

[0521] 在甲基 -3-(4-(5- 氯 -2-(2- 氯 -4-(N-(2,4- 二甲氧基苄基）-N-(1,2,4- 噻二唑 -5- 基）氨磺酰）-5- 氟苯氧基）苯基）吡啶酰胺基）丙酸甲酯）(1.0g,1.28mmol) 的 THF(10mL) 的溶液中添加一水合氢氧化锂 (0.27g,6.43mmol) 的水 (5ml) 的溶液。所得反应混合物允许在室温下搅拌 3 小时。在完成反应之后，将冰冷的水添加到反应混合物中，用 1N HCl1 酸化所得的混合物至 pH4-6。所得的酸性水溶液用乙酸乙酯 (3x 25ml) 提取。结合的有机提取物用水 (20ml)、盐水 (20ml) 冲洗，通过硫酸钠干燥，并且在真空下浓缩。粗产物通过使用正相硅胶的柱层析来纯化。所需的产物在大约 0-5％甲醇的二氯甲烷中洗脱。产物馏分蒸发得到 1g（产率 99％）所需的产物。LC-MS :m/z ＝ 762.8(M+H)。

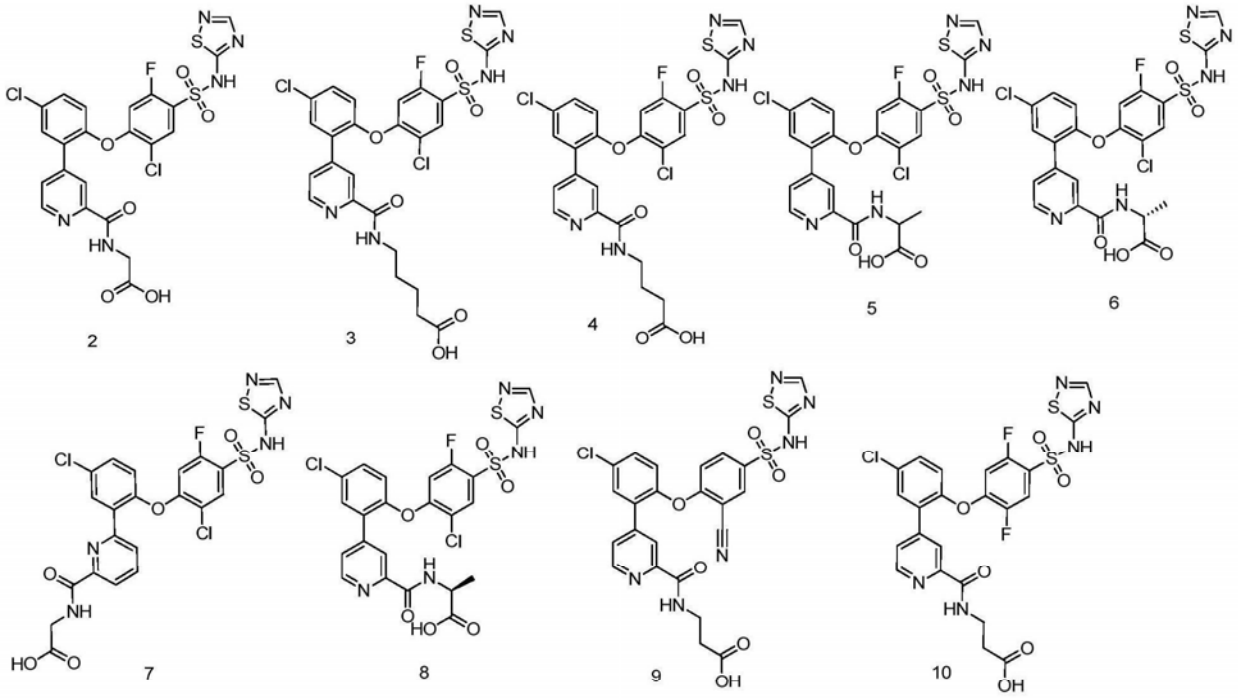
[0522] 步骤 7：制备 3-(4-(2-(4-(N-1,2,4- 噻二唑 -5- 基氨磺酰基）-2- 氯 -5- 氟苯氧基）-5- 氯苯基）吡啶酰胺基）丙酸

[0523] 在室温下，在 3-(4-(5- 氯 -2-(2- 氯 -4-(N-(2,4- 二甲氧基苄基）-N-(1,2,4- 噻二唑 -5- 基）氨磺酰）-5- 氟苯氧基）苯基）吡啶酰胺基）丙酸）(1.0g,1.3mmol) 的 DCM(10ml) 的溶液中逐滴加入盐酸的乙酸乙酯 (0.5ml) 的 4N 溶液。所得反应混合物进一步在室温下搅拌 2 小时。在完成反应之后，戊烷 (20ml) 添加到反应混合物中，得到固态沉淀物。因此获得的固体用戊烷 (15ml) 冲洗两次，并且在真空条件下干燥。使用 0.1％ HCl 的水 :乙腈流动相通过制备 HPLC 进一步纯化所得的粗料。纯的制备馏分蒸发得到 0.29g（产率 34％）所需的产物，为 HCl 的盐。LC-MS :m/z ＝ 612.9(M+H)。1H NMR(DMSO-d6), δ 9.03(br,1H),8.71(d,J ＝ 4.8Hz,1H),8.51(s,1H),8.20(s,1H),7.88(d,J ＝ 7.2Hz,1H),7.80(br,2H),7.60(d,J ＝ 8.4Hz,1H),7.28(d,J ＝ 8.4Hz,1H),7.22(d,J ＝ 10.8Hz,1H),4.01(br,2H)。

[0524] 根据实施例 1 描述的合成方案合成以下 9 种化合物。

[0525] 方案 6

[0526]



[0527] 实施例 2 :2-(4-(2-(4-(N-(1,2,4- 噻二唑 -5- 基) 氨磺酰基)-2- 氯 -5- 氟苯氧基)-5- 氯苯基) 吡啶酰胺基) 乙酸

[0528] 通过用甘氨酸甲酯盐酸盐替代步骤 4 中 β- 丙氨酸甲酯,根据实例 1 的合成所述的过程来合成化合物 2。LC-MS :m/z = 598.5(M+H)。1H NMR(DMSO-d6), δ 9.03(t,J = 6.0Hz,1H),8.71(d,J = 4.8Hz,1H),8.53(s,1H),8.19(s,1H),7.88(d,J = 7.2Hz,1H),7.78-7.81(m,2H),7.60(dd,J = 2.4,8.8Hz,1H),7.29(d,J = 8.8Hz,1H),7.22(d,J = 10.8Hz,1H),4.00(br,2H)。

[0529] 实施例 3 :5-(4-(2-(4-(N-(1,2,4- 噻二唑 -5- 基) 氨磺酰基)-2- 氯 -5- 氟苯氧基)-5- 氯苯基) 吡啶酰胺基) 戊酸。

[0530] 通过替换步骤 4 中的 β- 丙氨酸甲酯 5- 氨基戊酸甲酯,根据化合物 1 的合成过程来合成化合物 3。LC-MS :m/z = 640.2(M+H)。

[0531] 实施例 4 :4-(4-(2-(4-(N-(1,2,4- 噻二唑 -5- 基) 氨磺酰基)-2- 氯 -5- 氟苯氧基)-5- 氯苯基) 吡啶酰胺基) 丁酸

[0532] 通过用甲基 4- 氨基丁酸甲酯替代步骤 4 中的 β- 丙氨酸甲酯,根据化合物 1 的合成所述的过程来合成化合物 4。LC-MS :m/z = 626.6(M+H)。1H NMR(MeOH-d4), δ 8.65(d,J = 4.8Hz,1H),8.27(s,1H),8.26(s,1H),7.91(d,J = 6.8Hz,1H),7.74(d,J = 4.4Hz,1H),7.71(d,J = 2.4Hz,1H),7.60(dd,J = 2.8,8.8Hz,1H),7.24(d,J = 8.8Hz,1H),6.94(s,1H),6.78(d,J = 10.8Hz,1H),3.75(br,2H),2.41(t,J = 7.2Hz,2H),1.97(t,J = 7.2Hz,2H)。

[0533] 实施例 5 :(R)-2-(4-(2-(4-(N-1,2,4- 噻二唑 -5- 基氨磺酰)-2- 氯 -5- 氟苯氧基)-5- 氯苯基) 吡啶酰胺基) 丙酸

[0534] 通过用 DL- 丙氨酸甲酯盐酸盐替代步骤 4 中的 β- 丙氨酸甲酯,根据化合物 1 的合成所述的过程来合成化合物 5。LC-MS :m/z = 613.8(M+H)。1H NMR(MeOH-d4), δ 8.65(d,J = 5.6Hz,1H),8.27(s,1H),8.25(s,1H),7.90(d,J = 6.8Hz,1H),7.74(dd,J =

1.6,4.8Hz,1H),7.70(d,J = 2.4Hz,1H),7.59(dd,J = 2.8,8.8Hz,1H),7.23(d,J = 8.8Hz,1H),6.78(d,J = 10.8Hz,1H),4.63(q,J = 7.2Hz,1H),1.56(d,J = 7.6Hz,3H)。

[0535] 实施例 6 :(R)-2-(4-(2-(4-(N-1,2,4- 噻二唑 -5- 基氨磺酰)-2- 氯 -5- 氟苯氧基)-5- 氯苯基) 吡啶酰胺基) 丙酸

[0536] 通过用 DL- 丙氨酸甲酯盐酸盐替代步骤 4 中的 β - 丙氨酸甲酯,根据化合物 1 的合成所述的过程来合成化合物 6。LC-MS :m/z = 613.8(M+H)。1H NMR(MeOH-d4), δ 8.67(d,J = 5.2Hz,1H),8.27(s,1H),8.25(s,1H),7.91(d,J = 7.2Hz,1H),7.75(dd,J = 2.0,5.2Hz,1H),7.71(d,J = 2.8Hz,1H),7.60(dd,J = 2.4,8.4Hz,1H),7.24(d,J = 8.8Hz,1H),6.78(d,J = 10.8Hz,1H),4.63(q,J = 7.2Hz,1H),1.56(d,J = 7.6Hz,3H)。

[0537] 实施例 7 :2-(6-(2-(4-(N-(1,2,4- 噻二唑 -5- 基) 氨磺酰)-2- 氯 -5- 氟苯氧基)-5- 氯苯基) 吡啶酰胺基) 乙酸

[0538] 通过用 6- 氯甲基吡啶腈替代步骤 2 中的 4- 氯甲基吡啶腈,根据化合物 1 的合成所述的过程来合成化合物 7。LC-MS :m/z = 597.7(M+H)。1H-NMR(MeOD), δ 8.19(s,1H),8.00-8.07(m,4H),7.9s(d,J = 6.8Hz,1H),7.59(dd,J = 2.4,8.8Hz,1H),7.25(d,J = 8.8Hz,1H),6.72(d,J = 10.4Hz,1H),4.09(s,2H)。

[0539] 实施例 8 :(S)-2-(4-(2-(4-(N-1,2,4- 噻二唑 -5- 基氨磺酰)-2- 氯 -5- 氟苯氧基)-5- 氯苯基) 吡啶酰胺基) 丙酸

[0540] 通过用 L- 丙氨酸甲酯盐酸盐替代步骤 4 中的 β - 丙氨酸甲酯,根据化合物 1 的合成所述的过程来合成化合物 8。LC-MS :m/z = 612.6(M+H)。1H NMR(DMSO-d6), δ 8.85(d,J = 7.6Hz,1H),8.71(d,J = 5.6Hz,1H),8.52(s,1H),8.19(s,1H),7.88(d,J = 7.2Hz,1H),7.78-7.80(m,2H),7.60(dd,J = 2.4,8.8Hz,1H),7.28(d,J = 8.8Hz,1H),7.22(d,J = 10.8Hz,1H),4.47(q,J = 7.2Hz,1H),1.42(d,J = 7.2Hz,3H).

[0541] 实施例 9 :3-(4-(2-(4-(N-(1,2,4- 噻二唑 -5- 基) 氨磺酰基)-2- 氰基苯氧基)-5- 氯苯基) 吡啶酰胺基) 丙酸

[0542] 通过用 3- 氰基 -N-(2,4- 二甲氧基苄基)-4- 氟 -N-(1,2,4- 噻二唑 -5- 基) 苯磺酰胺替代步骤 5 中的 5- 氯 -N-(2,4- 二甲氧基)-2,4- 二氟 -N-(1,2,4- 噻二唑 -5- 基) 苯磺酰胺,根据化合物 1 的合成所述的过程来合成化合物 9。LC-MS :m/z = 584.8(M+H)。1H-NMR(MeOD), δ 8.63(d,J = 4.81H),8.23(s,1H),8.19(s,1H),8.14(d,J = 2.0Hz,1H),7.95(dd,J = 2.4,8.8Hz,1H),7.74-7.76(m,2H),7.63(dd,J = 2.4,8.8Hz,1H),6.97(d,J = 10.0Hz,1H),3.68(t,J = 6.8Hz,2H),2.65(t,J = 6.8Hz,2H)。

[0543] 实施例 10 :3-(4-(2-(4-(N-(1,2,4- 噻二唑 -5- 基) 氨磺酰基)-2,5- 二氟苯氧基)-5- 氯苯基) 吡啶酰胺基) 丙酸

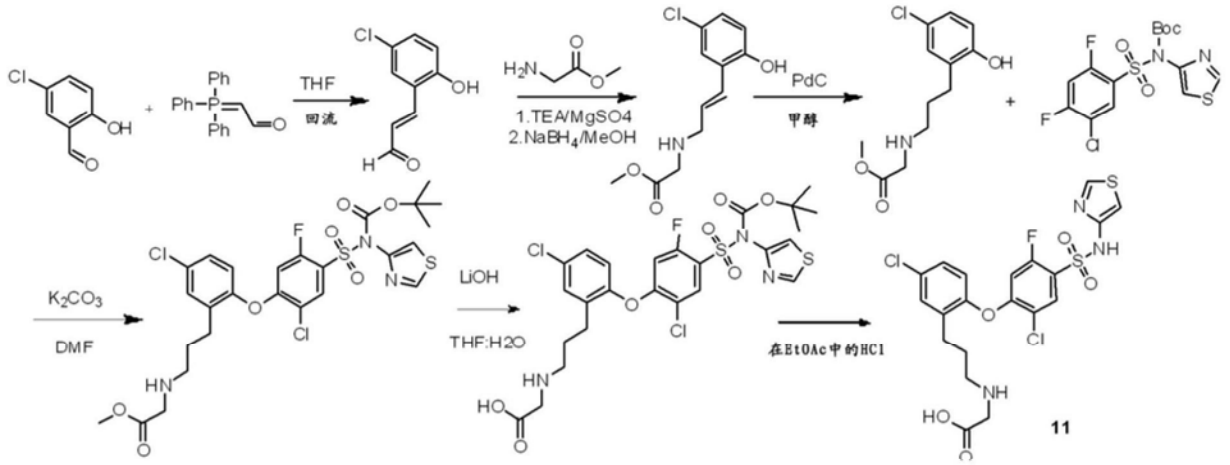
[0544] 通过用 N-(2,4- 二甲氧基苄基)-2,4,5- 三氟 -N-(1,2,4- 噻二唑 -5- 基) 苯磺酰胺替代步骤 5 中的 5- 氯 -N-(2,4- 二甲氧基)-2,4- 二氟 -N-(1,2,4- 噻二唑 -5- 基) 苯磺酰胺,根据化合物 1 的合成所述的过程来合成化合物 10。LC-MS :m/z = 595.8(M+H)。1H-NMR(MeOD), δ 8.66(d,J = 4.81H),8.28(s,1H),8.26(s,1H),7.69-7.77(m,3H),7.56(dd,J = 2.8,8.8Hz,1H),6.94(dd,J = 6.4,10.0Hz,1H),3.70(t,J = 6.4Hz,2H),2.67(t,J = 6.8Hz,2H)。

[0545] 实施例 11 :制备 2-(3-(5- 氯 -2-(2- 氯 -5- 氟 -4-(N- 噻唑 -4- 基氨磺酰基) 苯

氧基）苯基）丙基氨基）乙酸

[0546] 方案 7

[0547]



[0548] 步骤 1：制备 3-(5- 氯 -2- 羟基苯基）丙烯醛

[0549] 在室温下，在 5- 氯 -2- 羟基苯甲醛 (20g，127mmol) 的 THF(300ml) 的溶液中添加（甲酰基亚甲基）三苯基正膦 (43g，140mmol)。所得的反应混合物在 100℃下回流 20 小时。将该反应混合物冷却至室温，并且用水 (200ml) 和乙酸乙酯 (3×250ml) 提取。结合的有机相用水 (200ml)、盐水 (200ml) 冲洗，通过硫酸钠干燥，并且在真空下浓缩以获得所需的粗产物。使用正相硅胶通过柱层析纯化粗产物。所需的产物在大约 20-30％乙酸乙酯的己烷中洗脱。产物馏分蒸发得到黄色固态的 20g（产率 87％）的所需的化合物。LC-MS :m/z ＝ 183.4(M+H)。

[0550] 步骤 2：制备甲基 2-(3-(5- 氯 -2- 羟基苯基）烯丙基氨基）乙酸酯

[0551] 在室温下，在 3-(5- 氯 -2- 羟苯基）丙烯醛 (5g，27mmol) 和甘氨酸甲酯盐酸盐 (4.1g，32mmol) 的二氯甲烷 (80ml) 的溶液中添加硫酸镁 (6g，50mmol) 和三乙基胺 (12ml，82mmol)。上述反应混合物在室温下搅拌 18 小时。所得的反应混合物然后在真空下浓缩。因此获得的浓缩物溶解在甲醇 (50ml) 中，并且冷却至 5-10℃的温度。在上述混合物中，在反应混合物的添加温度维持在 10-20℃期间，在 20 分钟的时间段内添加小部分的硼氢化钠 (3.0g，82mmol)。在室温下搅拌该反应混合物 2 小时并且在真空下浓缩。将水 (100ml) 添加到上述粗物料并且所得的混合物用乙酸乙酯 (3×100ml) 提取。结合的有机提取物用水 (50ml)、盐水 (50ml) 冲洗，通过硫酸钠干燥，并且在真空下浓缩以获得所需的粗产物。使用正相硅胶通过柱层析纯化粗产物。所需的产物在大约 1-5％甲醇的二氯甲烷中洗脱。产物馏分蒸发得到 4g（产率 58％）黄色固态的所需化合物。LC-MS :m/z ＝ 256.43(M+H)。

[0552] 步骤 3：制备甲基 2-(3-(5- 氯 -2- 羟基苯基）丙基氨基）乙酸酯

[0553] 在甲基 2-(3-(5- 氯 -2- 羟基苯基）烯丙基氨基）乙酸酯 (3.5g，13.6mmol) 的甲醇 (80ml) 的溶液中小心地添加具有 50％水分 (0.145g，1.3mmol) 的 10％碳负载钯。然后在室温下将氢气在 30 分钟的持续时间内鼓泡到反应混合物中。在完成反应之后，将反应混合物通过硅藻土过滤。用一些量的甲醇小心地冲洗硅藻土床。因此获得的滤液在真空下浓缩以提供 3g（产率 85％）为无色液体的化合物，并且在下一步中按原样使用。LC-MS :m/z

＝ 258.5(M+H)。

[0554] 步骤 4:制备甲基 2-(3-(2-(4-(N-(叔丁氧基羰基)-N-(噻唑 -4- 基)氨磺酰)-2- 氯 -5- 氟苯氧基)-5- 氯苯基)丙基氨基)醋酸酯

[0555] 在氮气气氛且在室温下,在甲基 2-(3-(5- 氯 -2- 羟苯基)丙基氨基)醋酸酯(0.7g,2.7mmol)的 DMF(8ml)的溶液中添加一份 K_2CO_3(1.2g,8.1mmol)。然后在室温下搅拌所得反应混合物 15 分钟。在室温下,在上述化合物中添加叔丁基 -5- 氯 -2,4- 二氟苯基磺酰基(噻唑 -4- 基)氨基甲酸酯(1.22g,2.9mmol),在室温下搅拌所得的反应混合物 3 小时。在完成反应之后,添加水(10ml),然后用乙酸乙酯(3×25ml)提取所得混合物。用水(20ml)、盐水(20ml)洗涤结合的有机提取物,通过硫酸钠干燥,并且在真空下浓缩。使用正相硅胶通过柱层析纯化粗产物。所需产物在大约 20-25%乙酸乙酯的己烷中洗脱。产物馏分蒸发得到固态的 0.6g(产率 36%)所需化合物。LC-MS :m/z ＝ 648.4(M+H)。

[0556] 步骤 5:制备 2-(3-(2-(4-(N-(叔丁氧基羰基)-N-(噻唑 -4- 基)氨磺酰)-2- 氯 -5- 氟苯氧基)-5- 氯苯基)丙基氨基)乙酸

[0557] 在室温下,在甲基 2-(3-(2-(4-(N-(叔丁氧基羰基)-N-(噻唑 -4- 基)氨磺酰)-2- 氯 -5- 氟苯氧基)-5- 氯苯基)丙基氨基)乙酸乙酯(0.6g,0.9mmol)的 THF(10mL)的溶液中添加一水合氢氧化锂(0.0529,4.6mmol)的水(6ml)的溶液。所得的反应混合物在室温下搅拌 3 小时。在完成反应之后,将冰冷的水(15ml)添加到反应混合物中,然后用含水的 1N 盐酸酸化所得的混合物至 pH 4-6。所得的酸性水溶液用乙酸乙酯(3×25ml)提取。用水(20ml)、盐水(20ml)洗涤结合的有机提取物,通过硫酸钠干燥,并且在真空下浓缩以提供 0.5g(产率 85%)白色固态的化合物。在下一步中按原样使用此材料。

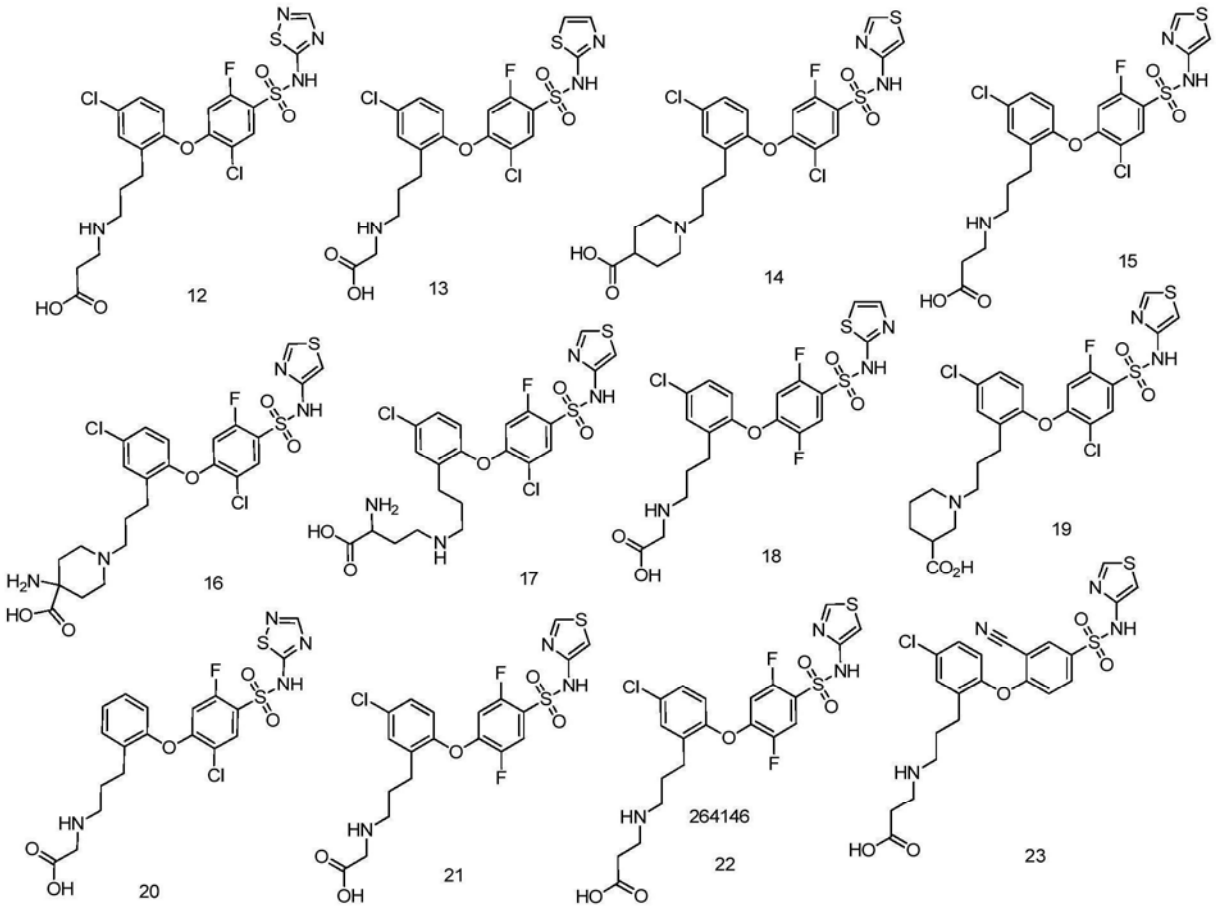
[0558] 步骤 6:制备 2-(3-(5- 氯 -2-(2- 氯 -5- 氟 -4-(N- 噻唑 -4- 基氨磺酰基)苯氧基)苯基)丙基氨基)乙酸

[0559] 在室温下,在 2-(3-(2-(4-(N-(叔丁氧基羰基)-N-(噻唑 -4- 基)氨磺酰)-2- 氯 -5- 氟苯氧基)-5- 氯苯基)丙基氨基)乙酸(0.5g,0.78mmol)的二氯甲烷(15ml)的溶液中逐滴添加盐酸的乙酸乙酯(0.5ml)的 4N 溶液。在室温下搅拌所得的反应混合物 2 小时。在完成反应之后,将戊烷(20ml)添加到反应混合物中,得到固态沉淀物。滗出溶剂层,用戊烷(15ml)洗涤由此获得的固体物两次,并且在真空条件下干燥。使用 0.1%盐酸的水 :乙腈流动相,通过制备 HPLC 进一步纯化所得的粗料。从制备的 HPLC 获得的纯产物馏分蒸发提供所需的产物(0.16g,38%产率)的盐酸盐。LC-MS :m/z ＝ 533.9(M+H)。1H-NMR(MeOD), δ 8.77(d,J ＝ 2.4Hz,1H),8.03(d,J ＝ 6.8Hz,1H),7.49(d,J ＝ 2.4Hz,1H),7.37(dd,J ＝ 2.8,8.8Hz,1H),7.12(d,J ＝ 2.4Hz,1H),7.03(d,J ＝ 8.8Hz,1H),6.76(d,J ＝ 10.8Hz,1H),3.8(s,2H),3.09-3.05(m,2H),2.68(t,J ＝ 7.6Hz,2H),2.04-2.01(m,2H)。

[0560] 根据实例 11 描述的合成方案合成化合物 12-32。

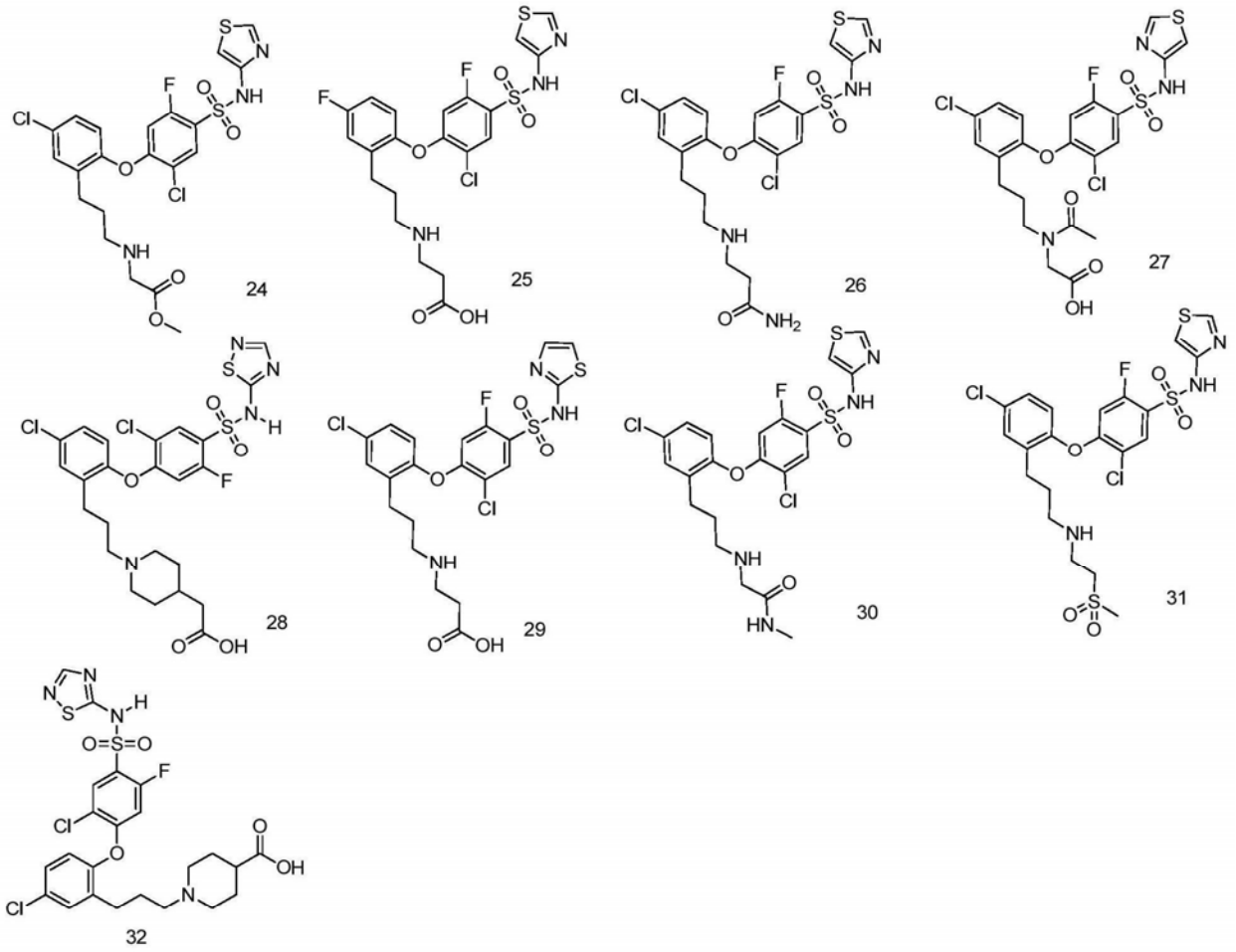
[0561] 方案 8

[0562]



[0563] 方案 9

[0564]



[0565] 实施例 12 :3-((3-(2-(4-(N-(1,2,4- 噻二唑 -5- 基) 氨磺酰基)-2- 氯 -5- 氟苯氧基)-5- 氯苯基) 丙基) 氨基) 丙酸

[0566] 通过用 β- 丙氨酸甲酯替代步骤 2 中的甘氨酸甲酯,并且用 5- 氯 -N-(2,4- 二甲氧基)-2,4- 二氟 -N-(1,2,4- 噻二唑 -5- 基) 苯磺酰胺替代步骤 4 中的叔丁基 -5- 氯 -2,4- 二氟苯基磺酰基 (噻唑 -4- 基) 氨基甲酸酯,根据化合物 11 的合成所述的过程来合成化合物 12。LC-MS :m/z = 549.6(M+H)。1H-NMR(MeOD), δ 8.27(s,1H),8.05(d,J = 7.2Hz,1H),7.49(d,J = 2.4Hz,1H),7.36(dd,J = 2.8,8.8Hz,1H),7.03(d,J = 8.8Hz,1H),6.78(d,J = 6.4Hz,1H),3.26(t,J = 6.4Hz,2H),3.08(t,J = 7.6Hz,2H),2.68-2.75(m,4H),2.01-2.06(m,2H)。

[0567] 实施例 13 :2-((3-(5- 氯 -2-(2- 氯 -5- 氟 -4-(N-(噻唑 -2- 基) 氨磺酰基) 苯氧基) 苯基) 丙基) 氨基) 乙酸

[0568] 通过用 5- 氯 -N-(2,4- 二甲氧基)-2,4- 二氟 -N-(噻唑 -2- 基) 苯磺酰胺替代步骤 4 中的叔丁基 -5- 氯 -2,4- 二氟苯基磺酰基 (噻唑 -4- 基) 氨基甲酸酯,根据化合物 11 的合成所述的过程来合成化合物 13。LC-MS :m/z = 533.8(M+H)。1H-NMR(MeOD), δ 7.94(d,J = 6.8Hz,1H),7.52(d,J = 5.8,1H),7.35-7.38(dd,J = 2.4,8.8Hz,1H),7.33(d,J = 4.4Hz,1H),7.11(d,J = 8.8Hz,1H),6.91-6.94(m,2H),3.60(s,2H),2.80(m,2H),2.56(m,2H),1.99(m,2H)。

[0569] 实施例 14 :1-(3-(5- 氯 -2-(2 氯 -5- 氟 -4-(N-(噻唑 -4- 基) 氨磺酰基) 苯氧基) 苯基) 丙基) 哌啶)4- 羧酸

[0570] 通过用甲基哌啶-4-羧酸乙酯替代步骤2中的甘氨酸甲酯，根据化合物11的合成所述的过程来合成化合物14。LC-MS：m/z = 589.8(M+H)。

[0571] 实施例15：3-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)丙酸

[0572] 通过用β-丙氨酸甲酯替代步骤2中的甘氨酸甲酯，根据化合物11的合成所述的过程来合成化合物15。LC-MS：m/z = 547.8(M+H)。1H-NMR(MeOD)，δ8.77(d,J = 2.0Hz,1H),8.03(d,J = 10.8Hz,1H),7.49(d,J = 2.4Hz,1H),7.35-7.38(m,1H),7.12(d,J = 2.8Hz,1H),7.03(d,J = 8.4Hz,1H),6.76(d,J = 10.4Hz,1H),3.26(br,2H),3.07(br,2H),2.67-2.76(m,4H),2.02(br,2H)。

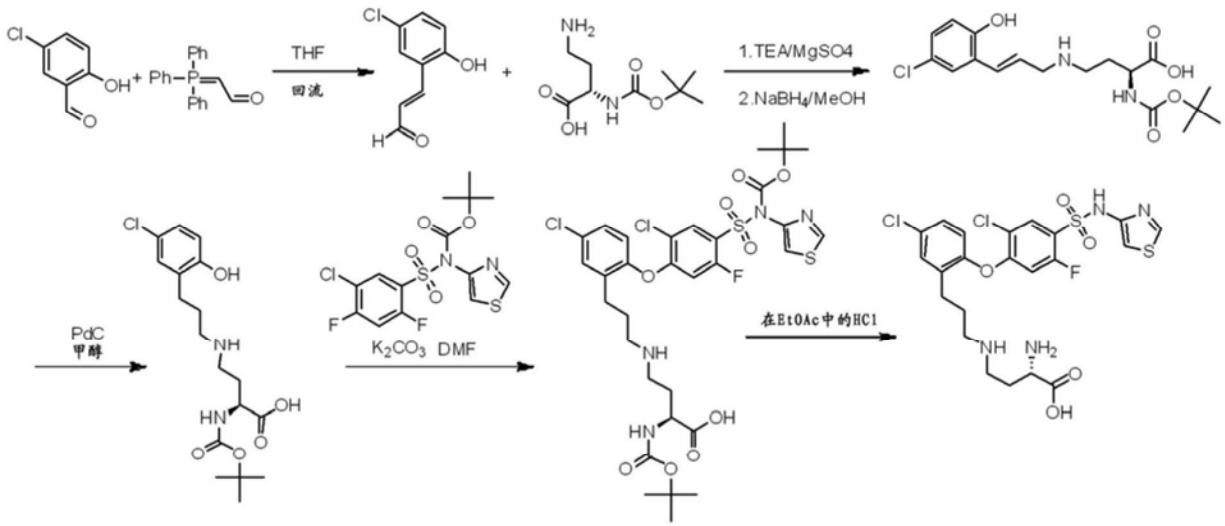
[0573] 实施例16：4-氨基-1-(3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)哌啶-4-羧酸

[0574] 通过用甲基4-((叔丁氧基羰基)氨基)哌啶-4-羧酸乙酯替代步骤2中的甘氨酸甲酯，根据化合物11的合成所述的过程来合成化合物16。LC-MS：m/z = 602.8(M+H)。1H-NMR(MeOD)，δ8.77(d,J = 2.0Hz,1H),8.02(d,J = 7.2Hz,1H),7.52(d,J = 2.8Hz,1H),7.36-7.38(dd,J = 2.8,8.8Hz,1H),7.12(d,J = 2.0Hz,1H),7.03(d,J = 8.4Hz,1H),6.77(d,J = 10.4Hz,1H),3.25-3.70(m,6H)2.67-2.71(m,2H),2.50(br,2H),2.27(br,2H),2.12(br,2H)。

[0575] 实施例17：2-氨基-4-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)丁酸

[0576] 方案10

[0577]



[0578] 步骤1：制备(S)-4-氨基-2-(叔丁氧基羰)丁酸

[0579] 在(S)-5-氨基-2-(叔丁氧基羰基)-5-氧代戊酸(2g,8.1mmol)的DMF：水(1:1,v/v,18ml)的溶液中添加吡啶(1.3ml,16.2mmol)。然后在室温下搅拌所得反应混合物5-10分钟。添加二乙酸碘苯(3.92g,12.1mmol)并且进一步搅拌4小时。在完成反应之后，添加去离子水(100ml)，然后用乙酸乙酯(3×100ml)提取混合物。用去离子水(100ml)、盐水(100ml)洗涤结合的有机提取物，通过硫酸钠干燥，并且在真空下浓缩以获得所需的粗产物。通过用二乙醚磨碎来纯化粗产物。产物馏分蒸发得到1.1g(产率62％)棕色固态

的所需化合物。LC-MS :m/z = 219.1(M+H)。

[0580] 步骤 2:制备 (E)-3-(5- 氯 -2- 羟基苯基) 丙烯醛

[0581] 在室温下,在 5- 氯 -2- 羟基苯甲醛 (20g,127mmol) 的 THF(300ml) 的溶液中添加 (甲酰基亚甲基) 三苯基正膦 (43g,140mmol)。然后在 100℃下回流所得的反应混合物 20 小时。在完成反应之后,允许反应混合物冷却到室温。添加去离子水 (200ml),然后用乙酸乙酯 (3×250ml) 提取所得混合物。用去离子水 (200ml)、盐水 (200ml) 洗涤结合的有机提取物,通过硫酸钠干燥,并且在真空下浓缩以获得所需的粗产物。使用正相硅胶通过柱层析纯化粗产物。所需的产物在大约 20-30% 乙酸乙酯的己烷中洗脱。产物馏分蒸发得到 20g(产率 87%) 的黄色固态的所需化合物。LC-MS :m/z = 183.4(M+H)。

[0582] 步骤 3:(S,E)-2-(叔丁氧基羰基氨基)-4-(3-(5- 氯 -2- 羟基苯基) 烯丙基氨基) 丁酸

[0583] 在室温下,在 3-(5- 氯 -2- 羟基苯基) 丙烯醛 (0.5g,3.2mmol) 和 (S)-4- 氨基 -2-(叔丁氧基羰基氨基) 丁酸 (0.769g,3.52mmol) 的二氯甲烷 (80ml) 的溶液中添加硫酸镁 (0.77g,6.4mmol) 和三乙基胺 (1.34ml,9.615mmol)。在室温下搅拌上述反应混合物 12 小时。然后在真空下浓缩所得的反应混合物。因此获得的浓缩物溶解在甲醇 (20ml) 中,并且冷却至 5-100℃的温度。在上述混合物中,将反应混合物的添加温度维持在 10-20℃期间,在 10 分钟的时间段内添加小部分的硼氢化钠 (0.36g,9.61mmol)。在完成添加之后,在室温下搅拌所得反应混合物 2 小时。在完成反应之后,在真空下浓缩反应混合物。将去离子水 (40ml) 添加到上述粗物料并且用乙酸乙酯 (3×60ml) 提取所得的混合物。用去离子水 (50ml),、盐水 (50ml) 洗涤结合的有机提取物,通过硫酸钠干燥,并且在真空下浓缩以获得所需的粗产物。使用正相硅胶通过柱层析纯化粗产物。所需的产物在大约 1-5% 甲醇的二氯甲烷中洗脱。产物馏分蒸发得到 0.4g(产率 32.5%) 棕色液态的所需的化合物。LC-MS :m/z = 385.2(M+H)。

[0584] 步骤 4:(S)-2-(叔丁氧基羰基氨基)-4-(3-(5- 氯 -2- 羟基苯基) 丙基氨基) 丁酸

[0585] 在 (S,E)-2-(叔丁氧基羰基)-4-(3-(5- 氯 -2- 羟基苯基) 烯丙基氨基) 丁酸 (0.4g,13.6mmol) 的甲醇 (10ml) 的溶液中小心地添加具有 50% 水分 (0.120g,1.3mmol) 的 10% 碳负载钯。然后在室温下将氢气在 15-20 分钟的持续时间内鼓泡到反应混合物中。在完成反应之后,将反应混合物通过白色硅藻土载体过滤。用一些量的甲醇小心地冲洗硅藻土床。因此获得的滤液在真空下浓缩以提供 0.35g(产率 87.06%) 无色液体的所需化合物。LC-MS :m/z = 387.4(M+H)。

[0586] 注意 :对于这个特定的步骤,还观察到发生脱氯作用,其比例保持变化。因此谨慎地监测此步骤并且在完成时迅速进行后处理。

[0587] 步骤 5:(S)-4-(3-(2-(4-(N-(叔丁氧基羰基)-N-(噻唑 -4- 基) 氨磺酰)-2- 氯 -5- 氟苯氧基)-5- 氯苯基) 丙基氨基)-2-(叔丁氧基羰基氨基) 丁酸

[0588] 在氮气气氛且在室温下,在 (S)-2-(叔丁氧基羰基氨基)-4-(3-(5- 氯 -2- 羟基苯基) 丙基氨基) 丁酸 (0.350g,2.7mmol) 的 DMF(0.7ml) 的溶液中添加一份 K_2CO_3(0.375g,2.7mmol)。然后在室温下搅拌所得反应混合物 15 分钟。在上述混合物中添加叔丁基 -5- 氯 -2,4- 二氟苯基磺酰基 (噻唑 -4- 基) 氨基甲酸酯 (0.408g,0.99mmol),并

且在室温下搅拌所得的反应混合物 3 小时。在完成反应之后，添加去离子水 (20ml)，然后用乙酸乙酯 (3×30ml) 提取混合物。用冰冷的水 (100ml)、盐水 (50ml) 洗涤结合的有机提取物，通过硫酸钠干燥，并且在真空下浓缩。使用正相硅胶通过柱层析纯化粗产物。在大约 1-2％甲醇的二氯甲烷中洗脱所需的产物。产物馏分蒸发得到 0.4g(产率 56.8％) 棕色液态的所需化合物。LC-MS :m/z ＝ 777.6(M+H).

[0589] 步骤 6：制备 (S)-2- 氨基 -4-(3-(5- 氯 -2-(2- 氯 -5- 氟 -4-(N- 噻唑 -4- 基氨磺酰基) 苯氧基) 苯基) 丙基氨基) 丁酸

[0590] 在室温下，在 (S)-4-(3-(2-(4-(N-(叔丁氧基羰基)-N-(噻唑 -4- 基) 氨磺酰)-2- 氯 -5- 氟苯氧基)-5- 氯苯基) 丙基氨基)-2-(叔丁氧基羰基) 丁酸 (0.4g,0.78mmol) 的二氯甲烷 (10ml) 的溶液中逐滴添加盐酸的乙酸乙酯 (2ml) 的 4N 溶液。在室温下搅拌所得的反应混合物 2 小时。在完成反应之后，将戊烷 (20ml) 添加到反应混合物中，得到固态沉淀物。滗出溶剂层，用戊烷 (15ml) 冲洗由此获得的固体物两次，并且在真空条件下干燥。使用 0.1％甲酸的水 :乙腈流动相通过制备 HPLC 进一步纯化所得的粗料。从制备的 HPLC 获得的纯产物馏分蒸发提供所需的产物 (0.0253g,8.6％产率) 的盐酸盐。LC-MS :m/z ＝ 576.8(M+H)。

[0591] 实施例 18 :2-((3-(5- 氯 -2-(2,5- 二氟 -4-(N-(噻唑 -2- 基) 氨磺酰基) 苯氧基) 苯基) 丙基) 氨基) 乙酸

[0592] 通过用 N-(2,4- 二甲氧基苄基)-2,4,5- 三氟 -N-(噻唑 -2- 基) 苯磺替代步骤 4 中的叔丁基 -5- 氯 -2,4- 二氟苯基磺酰基 (噻唑 -4- 基) 氨基甲酸酯，根据化合物 11 的合成所述的过程来合成化合物 18。LC-MS :m/z ＝ 517.8(M+H)。1H-NMR(MeOD), δ 7.81-7.85(dd,J ＝ 6.4,10.4Hz,1H),7.46(d,J ＝ 6.4,1H),7.31-7.34(dd,J ＝ 2.8,8.8Hz,1H),7.17(d,J ＝ 4.8Hz,1H),6.99(d,J ＝ 8.4Hz,1H),6.86-6.90(dd,J ＝ 6.4,10.0Hz,1H),6.81(d,J ＝ 4.8Hz,1H),3.92(s,2H),3.08-3.12(m,2H),2.75(t,J ＝ 8.0Hz,2H),2.03-2.08(m,2H)。

[0593] 实施例 19 :1-(3-(5- 氯 -2-(2- 氯 -5- 氟 -4-(N-(噻唑 -4- 基) 氨磺酰基) 苯氧基) 苯基) 丙基) 哌啶)3- 羧酸

[0594] 通过用甲基哌啶 -3- 羧酸乙酯替代步骤 2 中的甘氨酸甲酯，根据化合物 11 的合成所述过程来合成化合物 19。LC-MS :m/z ＝ 589.8(M+H)。

[0595] 实施例 20 :2-((3-(2-(4-(N-(1,2,4- 噻二唑 -5- 基) 氨磺酰基)-2- 氯 -5- 氟苯氧基) 苯基) 丙基) 氨基) 乙酸

[0596] 通过用 2- 羟基苯甲醛替代步骤 1 中的 5- 氯 -2- 羟基苯甲醛，根据化合物 11 的合成所述过程来合成化合物 20。LC-MS :m/z ＝ 500.8(M+H)。1H-NMR(MeOD), δ 8.90(s,2H),8.51(s,1H),7.97(d,J ＝ 7.2Hz,1H),7.41-7.44(dd,J ＝ 1.6,7.2Hz,1H),7.26-7.34(m,2H),7.07(dd,J ＝ 1.2,8.0Hz,1H),6.81(d,J ＝ 10.8Hz,1H),3.89(s,2H),2.93(br,2H),2.57-2.61(m,2H),1.92(br,2H)。

[0597] 实施例 21 :2-((3-(5- 氯 -2-(2,5- 二氟 -4-(N-(噻唑 -4- 基) 氨磺酰基) 苯氧基) 苯基) 丙基) 氨基) 乙酸

[0598] 通过用叔丁基 -2,4,5- 三氟苯基磺酰基 (噻唑 -4- 基) 氨基甲酸酯替代步骤 4 中的叔丁基 -5- 氯 -2,4- 二氟苯基磺酰基 (噻唑 -4- 基) 氨基甲酸酯，根据化合物 11 的合成所述过程来合成化合物 21。LC-MS :m/z ＝ 517.8(M+H)。

1H-NMR(MeOD), δ8.77(d,J = 2.0Hz,1H),7.79-7.83(dd,J = 6.4,10.0Hz,1H),7.47(d,J = 2.4Hz,1H),7.32-7.35(dd,J = 2.4,8.4Hz,1H),7.11(d,J = 2.4Hz,1H),7.02(d,J = 8.8Hz,1H),6.85-6.89(dd,J = 6.4,10.4Hz,1H),3.92(s,2H),3.09-3.16(m,2H),2.73(t,J = 7.6Hz,2H),1.99-2.07(m,2H)。

[0599] 实施例22:3-((3-(5-氯-2-(2,5-二氟-4-(N-(噻唑-4-基)氨磺酰)苯氧基)苯基)丙基)氨基)丙酸

[0600] 通过用β-丙氨酸甲酯替代步骤2中的甘氨酸甲酯并且用叔丁基-2,4,5-三氟苯基磺酰基(噻唑-4-基)氨基甲酸酯替代步骤4中的叔丁基-5-氯-2,4-二氟苯基磺酰基(噻唑-4-基)氨基甲酸酯,根据化合物11的合成所述过程来合成化合物22。LC-MS:m/z = 531.8(M+H)。1H-NMR(MeOD), δ8.78(d,J = 2.4Hz,1H),7.79-7.83(dd,J = 6.4,10.4Hz,1H),7.47(d,J = 2.4Hz,1H),7.32-7.35(dd,J = 2.4,8.4Hz,1H),7.11(d,J = 2.4Hz,1H),7.01(d,J = 8.8Hz,1H),6.85-6.90(dd,J = 6.4,10.4Hz,1H),3.27(t,J = 6.8Hz,2H),3.07(t,J = 8.0Hz,2H),2.71-2.78(m,4H),1.97-2.05(m,2H)。

[0601] 实施例23:3-((3-(5-氯-2-(2-氰基-4-(N-(噻唑-4-基)氨磺酰)苯氧基)苯基)丙基)氨基)丙酸

[0602] 通过用β-丙氨酸甲酯替代步骤2中的甘氨酸甲酯并且用叔丁基(3-氰基-4-氟苯基)磺酰基(噻唑-4-基)氨基甲酸酯替代步骤4中的叔丁基-5-氯-2,4-二氟苯基磺酰基(噻唑-4-基)氨基甲酸酯,根据化合物11的合成所述过程来合成化合物23。LC-MS:m/z = 520.9(M+H)。1H-NMR(MeOD), δ8.77(d,J = 2.0Hz,1H),8.30(d,J = 2.0Hz,1H),8.03(dd,J = 2.4,9.2Hz,1H),7.52(d,J = 2.4Hz,1H),7.39(dd,J = 2.8,8.8Hz,1H),7.16(d,J = 2.0Hz,1H),7.14(s,1H),6.96(d,J = 9.2Hz,1H),3.09(t,J = 6.8Hz,2H),3.09(t,J = 8.0Hz,2H),2.76(t,J = 6.4Hz,2H),2.69(t,J = 8.0Hz,2H),1.99-2.07(m,2H)。

[0603] 实施例24:甲基2-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)苯基)丙基)氨基)乙酸

[0604] 在甲酯没有水解(步骤5)的情况下,根据化合物11的合成所述过程来合成化合物24。LC-MS:m/z = 548.4(M+H)。1H-NMR(MeOD), δ8.77(d,J = 2.4Hz,1H),8.02(d,J = 6.8Hz,1H),7.49(d,J = 2.4Hz,1H),7.35-7.38(dd,J = 2.4,8.4Hz,1H),7.12(d,J = 2.4Hz,1H),7.02(d,J = 8.8Hz,1H),6.75(d,J = 10.4Hz,1H),3.99(s,2H),3.85(s,3H),3.08-3.12(m,2H),2.68(t,J = 7.6Hz,2H),2.00-2.08(m,2H)。

[0605] 实施例25:3-((3-(2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧基)-5-氟苯基)丙基)氨基)丙酸

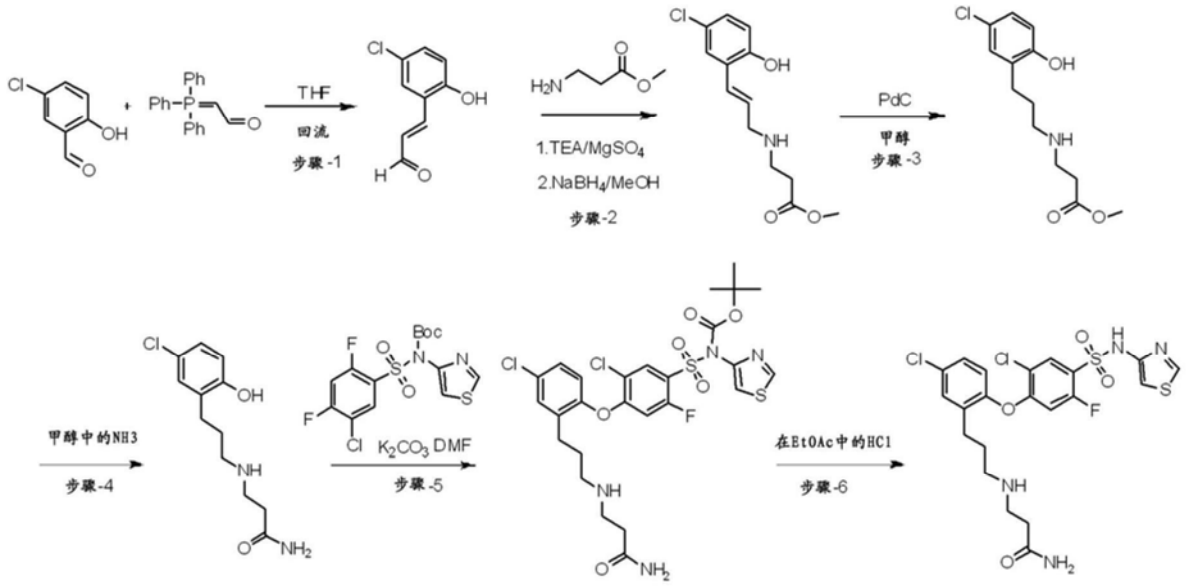
[0606] 通过用5-氟-2-羟基苯甲醛替代步骤1中的5-氯-2-羟基苯甲醛并且用β-丙氨酸甲酯替代步骤2中的甘氨酸甲酯,根据化合物11的合成所述的过程来合成化合物25。LC-MS:m/z = 531.9(M+H)。1H-NMR(MeOD), δ8.77(d,J = 2.4Hz,1H),8.01(d,J = 6.8Hz,1H),7.23(dd,J = 2.4,8.8Hz,1H),7.11-7.13(m,3H),6.65(d,J = 10.8Hz,1H),3.25(t,J = 6.8Hz,2H),3.06(t,J = 8.0Hz,2H),2.73(t,J = 6.4Hz,2H),2.66(t,J = 7.6Hz,2H),1.99-2.03(m,2H)。

[0607] 实施例26:3-((3-(5-氯-2-(2-氯-5-氟-4-(N-(噻唑-4-基)氨磺酰基)苯氧

基）苯基）丙基）氨基）丙酰胺

[0608] 方案 11

[0609]



[0610] 步骤 1：制备 3-(5- 氯 -2- 羟基苯基）丙烯醛

[0611] 在室温下，在 5- 氯 -2- 羟基苯甲醛 (20g，127mmol) 的 THF(300ml) 的溶液中添加（甲酰基亚甲基）三苯基正膦 (43g，140mmol)。然后在 100℃下回流所得的反应混合物 20 小时。在完成反应之后，使该反应混合物冷却到室温。添加去离子水 (200ml)，然后用乙酸乙酯 (3×250ml) 提取所得混合物。用水 (200ml)、盐水 (200ml) 洗涤结合的有机提取物，通过硫酸钠干燥，并且在真空下浓缩以获得所需的粗产物。使用正相硅胶通过柱层析纯化粗产物。在大约 20-30％乙酸乙酯的己烷中洗脱所需的产物。产物馏分蒸发得到 20g（产率 87％）的黄色固态的所需化合物。LC-MS :m/z ＝ 181.34(M-H)。

[0612] 步骤 2：制备 3-[3-(5- 氯 -2- 羟基苯基）烯丙基氨基］丙酸乙酯）

[0613] 在室温下，在 3-(5- 氯 -2- 羟基苯基）丙烯醛 (1.0g，5.47mmol) 和 β－丙氨酸甲酯盐酸盐 (0.917g，6.57mmol) 的 DCM(20ml) 的溶液中添加硫酸镁 (1.317g，1.09mmol) 和 TEA(2.3ml，16.41mmol)，并且在室温下搅拌所得的反应混合物 12 小时。然后在真空下浓缩反应混合物。因此获得的浓缩物溶解在甲醇 (20ml) 中，并且冷却至 5-10℃。在添加温度维持在 10-20℃之间期间，在 10-20 分钟的时间内向冷的反应混合物中添加小部分硼氢化钠 (0.620g，16.41mmol)。在完成添加之后，在室温下搅拌所得反应混合物 2 小时。在完成反应之后，在真空下浓缩该混合物。在所得的粗物料中加水 (50ml)，然后用 EtOAc(3×25ml) 提取混合物。用水 (20ml)、盐水 (20ml) 冲洗结合的有机提取物，通过硫酸钠干燥，并且在真空下浓缩以获得所需的粗产物。使用正相硅胶通过柱层析纯化粗产物。所需的产物在大约 1-5％甲醇的二氯甲烷中洗脱。产物馏分蒸发得到 0.9g（产率 61％）白色固态的所需化合物。LC-MS :m/z ＝ 270.6(M+H)。

[0614] 步骤 3：制备 3-[3-(5- 氯 -2- 羟基苯基）丙基氨基］丙酸甲酯）

[0615] 在 3-[3-(5- 氯 -2- 羟基苯基）烯丙基氨基］丙酸乙酯）(0.35g，1.3mmol) 的甲醇 (20ml) 的溶液中小心地添加具有 50％水分 (0.104g，0.065mmol) 的 10％碳负载钯。然后

在室温下将氢气鼓泡到反应混合物中 30 分钟。使用乙酸乙酯作为流动相在 TLC 上监测反应混合物。在完成反应之后，通过硅藻土过滤反应混合物。用一些量的甲醇小心地冲洗硅藻土床。在真空下浓缩因此获得的滤液以提供 0.3g（产率 85％）无色液体的所需化合物。m/z ＝ 272.6(M+H)。

[0616] 步骤 4：制备 3-[3-(5- 氯 -2- 羟基苯基）丙基氨基］丙酰胺）

[0617] 3-[3-(5- 氯 -2- 羟基苯基）丙基氨基］丙酸乙酯）(0.3g,1.08mmol) 的甲醇氨 (10mL) 的溶液在密封管 (35ml) 中加热到 100℃保温 12 小时。在完成反应之后，在真空下蒸发甲醇。使用正相硅胶通过柱层析纯化粗产物。在大约 30-40％乙酸乙酯的己烷中洗脱所需的产物。产物馏分蒸发得到 0.16g（产率 33.9％）无色液态的所需的化合物。m/z ＝ 257.2(M+H)。

[0618] 步骤 5：制备甲基 3-(3-(2-(4-(N-（叔丁氧基羰基）-N-（噻唑 -4- 基）氨磺酰）-2- 氯 -5- 氟苯氧基）-5- 氯苯基）丙基氨基）丙酸酯

[0619] 在氮气气氛下且在室温下，在 3-[3-(5- 氯 -2- 羟基苯基）丙基氨基］丙酸乙酯 (0.09g,0.35mmol) 的 DMF(2ml) 的溶液中添加一份 K_2CO_3(0.145,1.05mmol)。然后在室温下搅拌所得反应混合物 15 分钟。在上述混合物中添加叔丁基 -5- 氯 -2,4- 二氟苯基磺酰基（噻唑 -4- 基）氨基甲酸酯 (0.143g,0.35mmol)，并且在室温下搅拌所得的混合物 3 小时。在完成反应之后，添加水 (10ml)，然后用乙酸乙酯 (3×25ml) 提取混合物。用水 (20ml)、盐水 (20ml) 洗涤结合的有机提取物，通过硫酸钠干燥，并且在真空下浓缩。使用正相硅胶通过柱层析纯化粗产物。在大约 20-25％乙酸乙酯的己烷溶液中洗脱所需的产物。产物馏分蒸发得到 0.15g（产率 66.2％）固态的所需化合物。在不经过任何进一步提纯和分析的情况下，该材料用于下一个步骤。材料直接用于下一个步骤。

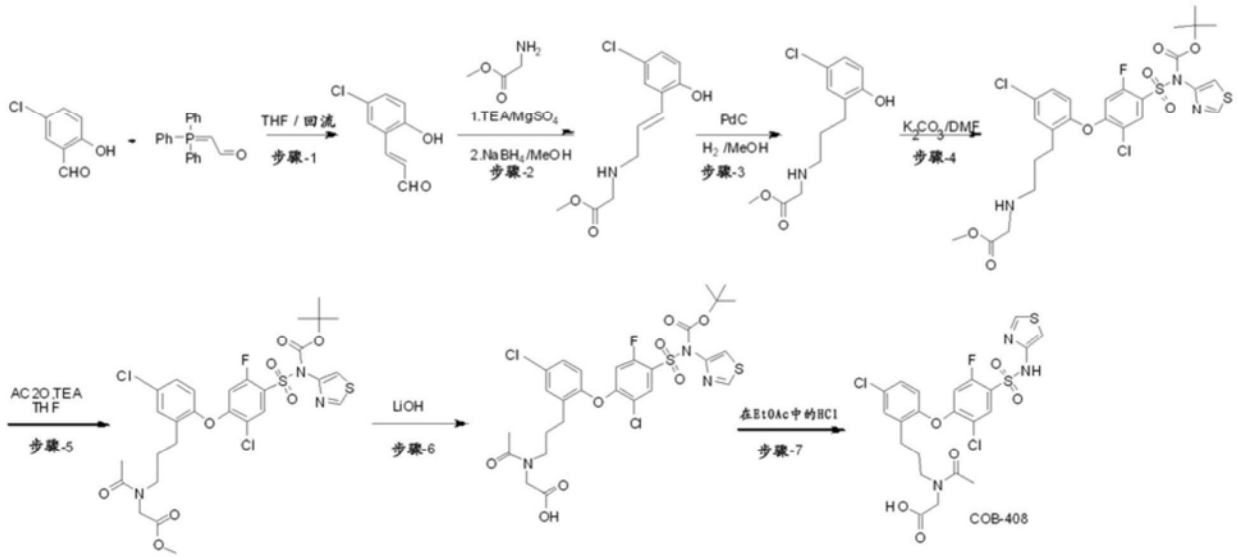
[0620] 步骤 6：制备 3-(3-(5- 氯 -2-(2- 氯 -5- 氟 -4-(N- 噻唑 -4- 基氨磺酰基）苯氧基）苯基）丙基氨基）丙酰胺氟苯基磺酰基（噻唑 -4- 基）氨基甲酸酯

[0621] 在室温下，在 3-(3-(2-(4-(N-（叔丁氧基羰基）-N-（噻唑 -4- 基）氨磺酰基）-2- 氯 -5- 氟苯氧基）-5- 氯苯基）丙基氨基）丙酸酯 (0.15g,0.23mmol) 的二氯甲烷 (5ml) 中逐滴加入盐酸的乙酸乙酯 (0.5ml) 的 4N 溶液。在室温下搅拌所得的反应混合物 2 小时。在完成反应之后，将戊烷 (20ml) 添加到反应混合物中，得到固态沉淀物。滗出溶剂层，用戊烷 (15ml) 冲洗因此获得的固体两次，并且在真空条件下干燥。使用 0.1％甲酸的水 :乙腈流动相，通过制备 HPLC 进一步纯化所得的粗料。从制备的 HPLC 获得的纯产物馏分蒸发提供所需的产物 (0.009g,7.1％产率）的盐酸盐。LC-MS :m/z ＝ 548.8(M+H)。1H-NMR(MeOD), δ 8.75(d,J ＝ 2.4Hz,1H),8.01(d,J ＝ 7.2Hz,1H),7.48(d,J ＝ 2.4Hz,1H),7.34-7.37(dd,J ＝ 2.4,8.8Hz,1H),7.06(d,J ＝ 2.4Hz,1H),7.01(d,J ＝ 8.4Hz,1H),6.73(d,J ＝ 10.4Hz,1H),3.22(t,J ＝ 6.4Hz,2H),3.02-3.06(m,2H),2.62-2.70(m,4H),1.99-2.03(m,2H)。

[0622] 实施例 27 :2-(N-(3-(5- 氯 -2-(2- 氯 -5- 氟 -4-(N-（噻唑 -4- 基）氨磺酰基）苯氧基）苯基）丙基）乙酰氨基）乙酸

[0623] 方案 12

[0624]



[0625] 步骤 1：制备 (E)-3-(5- 氯 -2- 羟基苯基) 丙烯醛

[0626] 在室温下，在 5- 氯 -2- 羟基苯甲醛 (20g，127mmol) 的 THF(300ml) 的溶液中添加 (甲酰基亚甲基) 三苯基正膦 (43g，140mmol)。然后在 100℃下所得的反应混合物回流 20 小时。在完成反应之后，使允许反应混合物冷却到室温。添加去离子水 (200ml)，然后用乙酸乙酯 (3×250ml) 提取所得混合物。用水 (200ml)、盐水 (200ml) 冲洗结合的有机提取物，通过硫酸钠干燥，并且在真空下浓缩以获得所需的粗产物。使用正相硅胶通过柱层析纯化粗产物。所需的产物在大约 20-30％乙酸乙酯的己烷中洗脱。产物馏分蒸发得到 20g(产率 87％) 黄色固态的所需化合物。LC-MS :m/z ＝ 183.4(M+H)。

[0627] 步骤 2：制备 (E)- 甲基 2-(3-(5- 氯 -2- 羟基苯基) 烯丙基氨基) 乙酸酯

[0628] 在室温下，在 (E)-3-(5- 氯 -2- 羟基苯基) 丙烯醛 (1.0g，5.4mmol) 和甘氨酸甲酯盐酸盐 (0.590g，6.55mmol) 的二氯甲烷 (20ml) 的溶液中添加硫酸镁 (1.5g，10.9mmol) 和三乙基胺 (2.28ml，16.38mmol)。在室温下搅拌上述反应混合物 12 小时。然后在真空下浓缩所得的反应混合物。将由此获得的浓缩物溶解在甲醇 (20ml) 中，并且冷却至 5-100℃的温度。在反应混合物的添加温度维持在 10-20℃期间，在 10 分钟的时间段内向上述混合物中添加小部分的硼氢化钠 (0.606g，16.38mmol)。在完成添加之后，使所得反应混合物在室温下搅拌 2 小时。在完成反应之后，在真空下浓缩反应混合物。将水 (40ml) 添加到上述粗物料并且用乙酸乙酯 (3x60ml) 提取所得的混合物。用水 (50ml)、盐水 (50ml) 洗涤结合的有机提取物，通过硫酸钠干燥，并且在真空下浓缩以获得所需的粗产物。使用正相硅胶通过柱层析纯化粗产物。在大约 2-3％甲醇的二氯甲烷中洗脱所需的产物。产物馏分蒸发得到 0.8g(产率 57.4％) 棕色液态的所需化合物。LC-MS :m/z ＝ 256.07(M+H)。

[0629] 步骤 3：制备甲基 2-(3-(5- 氯 -2- 羟基苯基) 丙基氨基) 乙酸酯

[0630] 在 (E)- 甲基 2-(3-(5- 氯 -2- 羟基苯基) 烯丙基) 乙酸酯 (0.8g，3.13mmol) 的甲醇 (50ml) 的溶液中小心地添加氢氧化钯 (0.199g，0.09mmol)。然后在室温下将氢气在 30 分钟的持续时间内鼓泡到反应混合物中。在完成反应之后，通过硅藻土过滤反应混合物。用一些量的甲醇小心地冲洗硅藻土床。因此获得的滤液在真空下浓缩以提供 0.7g(产率 86.81％) 无色液体的化合物。LC-MS :m/z ＝ 258.07(M+H).

[0631] 步骤 4：制备甲基 2-(3-(2-(4-(N-(叔丁氧基羰基)-N-(噻唑 -4- 基) 氨磺

酰)-2-氯-5-氟苯氧基)-5-氯苯基)丙基氨基)醋酸酯

[0632] 在氮气气氛下且在室温下,在甲基2-(3-(5-氯-2-羟苯基)丙基氨基)醋酸酯(0.7g,2.72mmol)的DMF(7ml)的溶液中添加一份K_2CO_3(1.12g,8.17mmol)。然后在室温下搅拌所得反应混合物15分钟。在上述混合物中添加叔丁基-5-氯-2,4-二氟苯基磺酰基(噻唑-4-基)氨基甲酸酯(1.22g,2.996mmol),并且在室温下搅拌所得的反应混合物3小时。在完成反应之后,添加水(20ml),然后用乙酸乙酯(3×50ml)提取混合物。用水(20ml)、盐水(20ml)洗涤结合的有机提取物,通过硫酸钠干燥,并且在真空下浓缩以提供0.54g(产率30.64%)白色固态的化合物。LC-MS:m/z = 646.20(M-H).

[0633] 步骤5:制备甲基2-(N-(3-(2-(4-(N-(叔丁氧基羰基)-N-(噻唑-4-基)氨磺酰)-2-氯-5-氟苯氧基)-5-氯苯基)丙基)乙酰氨基)乙酸酯。

[0634] 在甲基2-(3-(2-(4-(N-(叔丁氧基羰基)-N-(噻唑-4-基)氨磺酰)-2-氯-5-氟苯氧基)-5-氯苯基)丙基氨基)乙酸酯(0.35g,0.54mmol)的THF(5mL)的溶液中添加三乙胺(0.22ml,1.62mmol)。然后在0℃下搅拌所得反应混合物5-10分钟。在0℃下添加乙酸酐(0.102ml,1.08mmol)。然后在80℃下回流所得的反应混合物12小时。在反应混合物中添加水(30ml),并且用乙酸乙酯(3x50ml)提取所得的混合物。用水(30ml)、盐水(30ml)洗涤结合的有机提取物,通过硫酸钠干燥,并且在真空下浓缩以获得所需的粗产物。通过用二乙醚磨碎来纯化粗产物。产物馏分蒸发得到0.35g(产率94.01%)棕色固态的所需化合物。LC-MS:m/z = 690.5(M+H)。

[0635] 步骤6:制备2-(N-(3-(2-(4-(N-(叔丁氧基羰基)-N-(噻唑-4-基)氨磺酰)-2-氯-5-氟苯氧基)-5-氯苯基)丙基)乙酰氨基)乙酸

[0636] 在室温下,在甲基2-(N-(3-(2-(4-(N-(叔丁氧基羰基)-N-(噻唑-4-基)氨磺酰)-2-氯-5-氟苯氧基)-5-氯苯基)丙基)乙酰氨基)乙酸酯(0.35g,0.50mmol)的THF(5ml)的溶液中添加一水合氢氧化锂(0.212g,5.07mmol)的水溶液(0.5ml)。在室温下搅拌所得的反应混合物3小时。在完成反应之后,将冰冷的水(15ml)添加到反应混合物中,然后用含水的1N盐酸酸化所得的混合物至pH 4-6。用乙酸乙酯(3×25ml)提取所得的酸性水溶液。用水(20ml)、盐水(20ml)洗涤结合的有机提取物,通过硫酸钠干燥,并且在真空下浓缩以提供0.3g(产率87.49%)白色固态的化合物。在不经过任何进一步提纯和分析的情况下,该材料直接用于下一个步骤。LC-MS:m/z = 676.41(M+H)。

[0637] 步骤7:制备2-(N-(3-(5-氯-2-(2-氯-5-氟-4-(N-噻唑-4-基氨磺酰基)苯氧基)苯基)丙基)乙酰胺基)乙酸

[0638] 在室温下,在2-(N-(3-(2-(4-(N-(叔丁氧基羰基)-N-(噻唑-4-基)氨磺酰)-2-氯-5-氟苯氧基)-5-氯苯基)丙基)乙酰氨基)乙酸(0.3g,0.44mmol)的二氯甲烷(4ml)的溶液中逐滴盐酸的乙酸乙酯(1ml)的4N溶液。在室温下搅拌所得的反应混合物2小时。在完成反应之后,将戊烷(20ml)添加到反应混合物中,得到固态沉淀物。滗出溶剂层,用戊烷(15ml)冲洗因此获得的固体两次,并且在真空条件下干燥。使用0.1%盐酸的水:乙腈流动相通过制备HPLC进一步纯化所得的粗料。从制备的HPLC获得的纯产物馏分蒸发提供所需的产物(0.060g,23.47%产率)的盐酸盐。LC-MS:m/z = 575.92(M+H)。

[0639] 实施例28:2-(1-(3-(2-(4-(N-(1,2,4-噻二唑-5-基)氨磺酰基)-2-氯-5-氟苯氧基)-5-氯苯基)丙基)哌啶-4-基)乙酸

[0640] 通过用甲基 2-(哌啶 -4- 基)乙酸酯替代步骤 2 中的甘氨酸甲酯,并且用 5- 氯 -N-(2,4- 二甲氧基)-2,4- 二氟 -N-(1,2,4- 噻二唑 -5- 基)苯磺酰胺替代步骤 4 中的叔丁基 -5- 氯 -2,4- 二氟苯基磺酰基(噻唑 -4- 基)氨基甲酸酯,根据化合物 11 的合成所述过程来合成化合物 28。LC-MS :m/z = 601.2(M+H)。

[0641] 实施例 29 :3-((3-(5- 氯 -2-(2- 氯 -5- 氟 -4-(N-(噻唑 -2- 基)氨磺酰基)苯氧基)苯基)丙基)氨基)丙酸

[0642] 通过用 β- 丙氨酸甲酯替代步骤 2 中的甘氨酸甲酯,并且用 5- 氯 -N-(2,4- 二甲氧基)-2,4- 二氟 -N-(噻唑 -2- 基)苯磺酰胺替代步骤 4 中的叔丁基 -5- 氯 -2,4- 二氟苯基磺酰基(噻唑 -4- 基)氨基甲酸酯,根据化合物 11 的合成所述过程来合成化合物 29。LC-MS :m/z = 547.9(M+H)。1H-NMR(MeOD), δ 8.05(d,J = 6.8Hz,1H),7.49(d,J = 2.8Hz,1H),7.34(dd,J = 2.4,8.4Hz,1H),7.17(d,J = 4.4Hz,1H),7.02(d,J = 8.4Hz,1H),6.80(d,J = 4.4Hz,1H),6.75(d,J = 10.4Hz,1H),3.14(t,J = 6.4Hz,2H),3.04(t,J = 8.0Hz,2H),2.71(t,J = 8.0Hz,2H),2.49(t,J = 6.4Hz,2H),2.00-2.03(m,2H)。

[0643] 实施例 30 :2-((3-(5- 氯 -2-(2- 氯 -5- 氟 -4-(N-(噻唑 -4- 基)氨磺酰基)苯氧基)苯基)丙基)氨基)-N- 甲基乙酰胺

[0644] 通过用 2- 氨基 -N- 甲基乙酰胺代替步骤 2 中的甘氨酸甲酯,根据化合物 11 的合成所述的过程来合成化合物 30。LC-MS :m/z = 547.1(M+H)。1H-NMR(MeOD), δ 8.77(d,J = 2.4Hz,1H),8.01(d,J = 7.2Hz,1H),7.48(d,J = 2.4Hz,1H),7.35(dd,J = 2.4,8.4Hz,1H),7.10(d,J = 2.0Hz,1H),7.02(d,J = 8.8Hz,1H),6.73(d,J = 10.4Hz,1H),3.70(s,2H),2.97-3.02(m,2H),2.80(s,3H),2.65-2.69(m,2H),1.96-2.06(m,2H)。

[0645] 实施例 31 :5- 氯 -4-(4- 氯 -2-(3-((2-(甲磺酰基)乙基)氨基)丙基)苯氧基)-2- 氟 -N-(噻唑 -4- 基)苯磺酰胺

[0646] 通过用 2-(甲基磺酰基)乙胺代替步骤 2 中的甘氨酸甲酯,根据化合物 11 的合成所述的过程来合成化合物 31。LC-MS :m/z = 581.8(M+H)。1H-NMR(MeOD), δ 8.77(d,J = 2.4Hz,1H),8.02(d,J = 6.8Hz,1H),7.48(d,J = 2.4Hz,1H),7.36(dd,J = 2.8,8.8Hz,1H),7.10(d,J = 2.4Hz,1H),7.02(d,J = 8.4Hz,1H),6.73(d,J = 10.4Hz,1H),3.33-3.50(m,4H),3.03(s,3H),2.99-3.01(m,2H),2.65-2.68(m,2H),1.95-2.03(m,2H)。

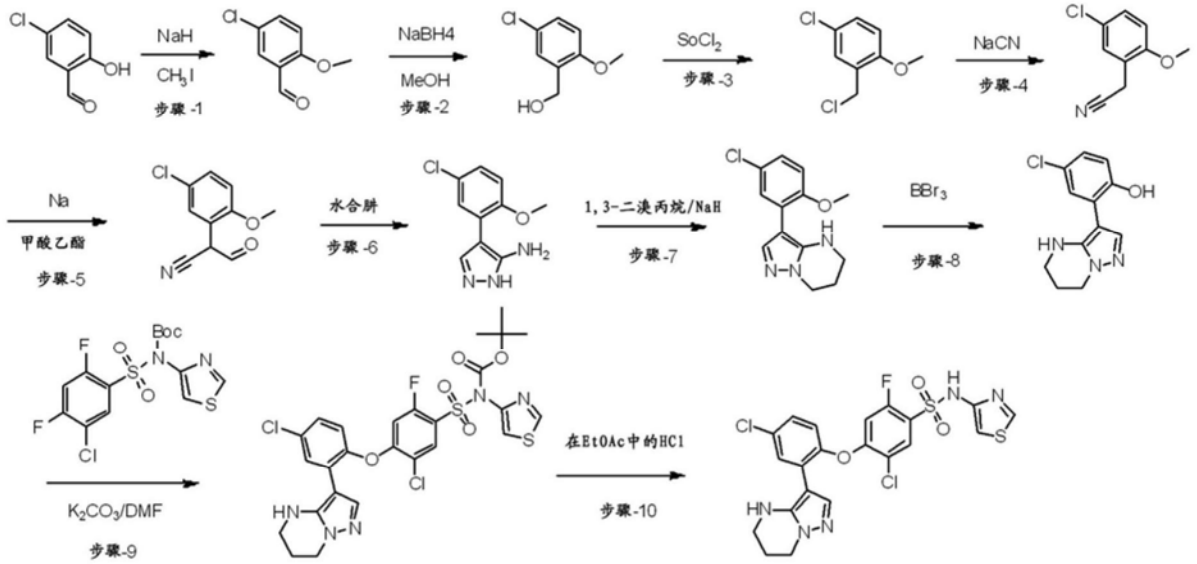
[0647] 实施例 32 :1-(3-(2-(4-(N-(1,2,4- 噻二唑 -5- 基)氨磺酰基)-2- 氯 -5- 氟苯氧基)-5- 氯苯基)丙基)哌啶 -4- 羧酸

[0648] 通过用甲基哌啶 -4- 羧酸乙酯替代步骤 2 中的甘氨酸甲酯,并且用 5- 氯 -N-(2,4- 二甲氧基)-2,4- 二氟 -N-(1,2,4- 噻二唑 -5- 基)苯磺酰胺替代步骤 4 中的叔丁基 -5- 氯 -2,4- 二氟苯基磺酰基(噻唑 -4- 基)氨基甲酸酯,根据化合物 11 的合成所述的过程来合成化合物 32。LC-MS :m/z = 589.6(M+H)。

[0649] 实施例 33 :5- 氯 -4-(4- 氯 -2-(4,5,6,7- 四氢吡唑并[1,5-α]嘧啶 -3- 基)苯氧基)-2- 氟 -N-(噻唑 -4- 基)苯磺酰胺

[0650] 方案 13

[0651]



[0652] 步骤 1：制备 5- 氯 -2- 甲氧基苯甲醛

[0653] 将 5- 氯 -2- 羟基苯甲醛 (20g,128mmol) 的 DMF(70mL) 的溶液冷却至 5-10℃的温度。在 20 分钟的时间内将氢化钠 (7.69g,192mmol) 以小部分添加到上述溶液中。然后在将上述反应混合物维持其温度低于 15℃时，将碘甲烷 (23.8ml,384mmol) 逐滴添加到上述反应混合物中。在完成添加之后，在室温下搅拌反应混合物 2 小时。此后，将反应混合物倒入冷饱和的氯化铵溶液 (250mL) 以获得白色沉淀物。滤出因此形成的沉淀物并且在真空下干燥。所得的固体用 100ml 戊烷 :二乙醚 (4:1) 磨碎以提供 18g(产率 82.58％) 白色固态的所需化合物。LC-MS :m/z ＝ 170.1(M+H)。

[0654] 步骤 2：制备 (5- 氯 -2- 甲氧基苯基) 甲醇

[0655] 将 5- 氯 -2- 甲氧基苯甲醛 (18g,105.8mmol) 的甲醇 (100mL) 的溶液冷却至 5-10℃的温度。在 30 分钟的时间内，向上述溶液中添加部分硼氢化钠 (11.8g,317mmol)。在完成添加之后，使所得反应混合物在室温下搅拌约 2 小时。使用乙酸乙酯 :己烷 (1 :1) 作为流动相在 TLC 上监测反应。在完成反应之后，在真空下浓缩混合物。在所得的粗块中添加冷水 (200ml) 以获得白色沉淀物。因此形成的沉淀物经过过滤并干燥以提供 16g(产率 87.8％) 白色固态的所需化合物。材料直接用于下一步。

[0656] 步骤 3：制备 4- 氯 -2-(氯甲基)-1- 甲氧基苯

[0657] 将 5- 氯 -2- 甲氧基苯基) 甲醇 (16g,94mmol) 的 DCM(100ml) 的溶液冷却至 5-10℃的温度。在 30 分钟的时间内，向上述溶液中逐滴添加亚硫酰氯 (11ml,140mmol)。在完成添加之后，在室温下搅拌所得反应混合物 4 小时。在完成反应之后，在真空下浓缩混合物。在所得的粗块中添加冷水 (150ml) 以获得白色沉淀物。因此形成的沉淀物被滤出并且在真空下干燥以提供 12g(产率 67.9％) 白色固态的所需化合物。材料直接用于下一步。

[0658] 步骤 4：制备 2-(5- 氯 -2- 甲氧基苯基) 乙腈

[0659] 在室温下在 4- 氯 -2-(氯甲基)-1- 甲氧基苯 (12g,63.15mmol) 的 DMSO(60mL) 的溶液中小心地添加氰化钠 (4.4g,95.6mmol)。然后将上述反应混合物加热到 100℃并保温 3 小时。在冷却至室温之后，将反应混合物倒入冷水 (200ml) 中以获得沉淀物。滤出因此形成的沉淀物并且在真空下干燥以提供米 10g(产率 87.46％) 白色固态的所需化合物。材料直接用于下一步。

[0660] 步骤 5：制备 2-(5- 氯 -2- 甲氧基苯基)-3- 氧代丙腈

[0661] 在室温下，在 2-(5- 氯 -2- 甲氧基苯基) 乙腈 (10g,47.84mmol) 的甲酸乙酯 (50mL) 的溶液中添加金属钠 (4.4g,95.6mmol)。将所得的反应混合物加热到 100℃并保温 3 小时。在完成反应之后，将所得的反应物冷却至室温，将水 (100ml) 和二氯甲烷 (100ml) 添加到反应混合物中，并且溶液在浓盐酸的帮助下调节到 pH-3。这些层分离，并且用二氯甲烷 (2×100ml) 提取含水的层。用饱和的含水的氯化钠溶液 (150ml) 洗涤结合的有机物，通过硫酸钠干燥，在真空下过滤并蒸发。使用正相硅胶通过柱层析纯化粗产物。在大约 0.7-0.9％甲醇的二氯甲烷中洗脱所需的产物。产物馏分蒸发得到 9g(产率 77.94％) 白色固态的所需化合物。LC-MS :m/z ＝ 208.0(M-H)。

[0662] 步骤 6：制备 4-(5- 氯 -2- 甲氧基苯基)-1H- 吡唑 -5- 胺

[0663] 在室温下，在 2-(5- 氯 -2- 甲氧基苯基)-3- 氧代丙腈 (9g,43mmol) 的乙醇 (90mL) 的溶液中添加水合肼 (4.3g,86.12mmol) 和冰醋酸 (2.7mL,51.6mmol)。然后在回流情况下加热反应混合物 3 小时。在完成反应之后，将反应混合物冷却至室温，并且碳酸氢钠水溶液 (150ml) 淬灭。用二氯甲烷 (3×100ml) 提取所得的化合物。用盐水洗涤结合的有机层，通过硫酸钠干燥，并且在真空下浓缩。使用正相硅胶通过柱层析纯化粗产物。所需的产物在大约 0.9-1.1％甲醇的二氯甲烷中洗脱。产物馏分蒸发得到 7g(产率 72.8％) 白色固态的所需化合物。LC-MS :m/z ＝ 224.1(M+H)。

[0664] 步骤 7：制备 3-(5- 氯 -2- 甲氧基苯基)-4,5,6,7- 四氢吡唑并 [1,5-a] 嘧啶

[0665] 将 4-(5- 氯 -2- 甲氧基苯基)-1H- 吡唑 -5- 胺 (3g,13.45mmol) 的干 DMF(15mL) 的溶液冷却至 5-10℃的温度。在 30 分钟的时间内将氢化钠 (0.806g,20.17mmol) 以小部分添加到上述溶液中。在 5-10℃下搅拌所得的反应混合物 30 分钟，此后在上述化合物中逐滴添加 1,3- 二溴丙烷 (1.78ml,17.48mmol)。将所得的反应混合物加热到 100℃并保温 4 小时。在完成反应之后，用冷水 (100ml) 稀释溶液，并且用乙酸乙酯 (3×100ml) 提取产物。用盐水冲洗涤合的有机层，通过硫酸钠干燥，并且在真空下浓缩。使用正相硅胶通过柱层析纯化粗产物。所需的产物在大约 1.2-1.5％甲醇的二氯甲烷中洗脱。产物馏分蒸发得到 0.65g(产率 18.36％) 半固态的所需化合物。LC-MS :m/z ＝ 264.2(M+H)。

[0666] 步骤 8：制备 4- 氯 -2-(4,5,6,7- 四氢吡唑并 [1,5-a] 嘧啶 -3- 基) 苯酚

[0667] 将 3-(5- 氯 -2- 甲氧基苯基)-4,5,6,7- 四氢吡唑并 [1,5-a] 嘧啶 (0.65g,1.9mmol) 的二氯甲烷 (30mL) 的溶液冷却至 5-10℃的温度。在 30 分钟的时间内，向上述溶液中逐滴添加三溴化硼的二氯甲烷溶液 (4.7mL,4.75mmol)。在完成添加之后，在室温下搅拌所得反应混合物 4 小时。在完成反应之后，用冷水 (40mL) 稀释溶液，并且用乙酸乙酯 (3×30ml) 提取产物。用盐水洗涤结合的有机层，通过硫酸钠干燥，并且在真空下浓缩以提供 0.65g(产率 81.24％) 白色固态的所需化合物。LC-MS :m/z ＝ 250.2(M+H)。

[0668] 步骤 9：制备叔丁基 -5- 氯 -4-(4- 氯 -2-(4,5,6,7- 四氢吡唑并 [1,5-a] 嘧啶 -3- 基) 苯氧基)-2- 氟苯基磺酰基 (噻唑 -4- 基) 氨基甲酸酯

[0669] 在氮气气氛下且在室温下，在 4- 氯 -2-(4,5,6,7- 四氢吡唑并 [1,5-a] 嘧啶 -3- 基) 苯酚 (0.5g,2.008mmol) 的 DMF(8ml) 的溶液中添加一份 K_2CO_3(0.556g,4.016mmol))。然后在室温下搅拌所得反应混合物 15 分钟。在上述混合物中添加叔丁基 -5- 氯 -2,4- 二氟苯基磺酰基 (噻唑 -4- 基) 氨基甲酸酯 (0.989g,2.409mmol)，

并且在室温下搅拌所得的反应混合物 3 小时。在完成反应之后，添加水 (10ml)，然后用乙酸乙酯 (3×25ml) 提取混合物。用水 (20ml)、盐水 (20ml) 洗涤结合的有机提取物，通过硫酸钠干燥，并且在真空下浓缩。使用正相硅胶通过柱层析纯化粗产物。所需的产物在大约 40-50％乙酸乙酯的己烷中洗脱。产物馏分蒸发得到 0.4g（产率 31.18％）黄色固态的所需的化合物。LC-MS :m/z ＝ 640.1(M+H)。

[0670] 步骤 10：制备 5- 氯 -4-(4- 氯 -2-(4,5,6,7- 四氢吡唑并 [1,5-α] 嘧啶 -3- 基) 苯氧基)-2- 氟 -N-(噻唑 -4- 基) 苯磺酰胺

[0671] 在室温下，在叔丁基 -5- 氯 -4-(4- 氯 -2-(4,5,6,7- 四氢吡唑并 [1,5-a] 嘧啶 -3- 基) 苯氧基)-2- 氟苯基磺酰基 (噻唑 -4- 基) 氨基甲酸酯 (0.4g,0.626mmol) 的二氯甲烷 (15ml) 的溶液中逐滴添加盐酸的乙酸乙酯 (0.8ml) 的 4N 溶液。在室温下搅拌所得的反应混合物 2 小时。在完成反应之后，将戊烷 (20ml) 添加到反应混合物中，得到固态沉淀物。滗出溶剂层，用戊烷 (15ml) 冲洗因此获得的固体两次，并且在真空条件下干燥。使用 0.1％盐酸的水 :乙腈流动相通过制备 HPLC 进一步纯化所得的粗料。从制备的 HPLC 获得的纯产物馏分蒸发提供所需的产物 (0.130g,38.6％产率) 的盐酸盐。LC-MS :m/z ＝ 539.78(M+H)。1H NMR(400MHz, 甲醇 -d4) δ 8.76(d,J ＝ 2.4Hz,1H),8.02(s,1H),7.95(d,J ＝ 7.2Hz,1H),7.61(d,J ＝ 2.4Hz,1H),7.54(dd,J ＝ 2.4,8.4Hz,1H),7.27(d,J ＝ 8.4Hz,1H),7.09(d,J ＝ 2.0Hz,1H),6.62(d,J ＝ 10.8Hz,1H),4.14(t,J ＝ 6.0Hz,2H),3.40(t,J ＝ 5.6Hz,2H),2.14(p,J ＝ 6.0Hz,2H)。

[0672] 本文所述的实施方式仅仅旨在示例性的，并且本领域的技术人员应当认识到或者能在使用不超过常规实验的情况下确定本文所述的具体过程的许多等同形式。所有这些等同形式被认为在本发明的范围内并且由以下实施方式涵盖。

[0673] 本文引用的所有参考文献 (包括专利申请、专利和公开) 通过引用的方式全部并且为了所有目的并入本文中，如同每个单独的公开或专利或专利申请专门且单独地表明通过引用的方式为了所有目的全部并入本文中。