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(54) **Title:** SODIUM CHANNEL INHIBITORS AND METHODS OF DESIGNING SAME

(57) **Abstract:** The invention provides compounds of formulae I, II, IIa, and III, as described herein, and pharmaceutically acceptable salts thereof, as well as compositions containing such compounds and methods for using such compounds and compositions.

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SODIUM CHANNEL INHIBITORS AND METHODS OF DESIGNING SAME

CLAIM OF PRIORITY

[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. provisional application serial no. 63/236,594, filed on August 24, 2021, which application is incorporated herein by reference.

BACKGROUND

[0002] The present invention relates to organic compounds useful for therapy in a mammal, particularly a human, and in particular to inhibitors of sodium channel (*e.g.*, NaV1.7) that are useful for treating sodium channel-mediated diseases or conditions, such as pain, as well as other diseases and conditions associated with the modulation of sodium channels. The invention further includes methods of designing organic compounds that inhibit the NaV1.7 channel based on atom-resolution structures thereof, such as obtained by cryogenic electron microscopy ("Cryo-EM", or "cryoEM").

[0003] Voltage-gated sodium channels are transmembrane proteins that initiate action potentials in nerve, muscle and other electrically excitable cells, and are a necessary component of normal sensation, emotions, thoughts and movements (Catterall, W.A., *Nature* (2001), 409, 988-990). These channels contain a highly processed alpha subunit associated with auxiliary beta subunits. The pore-forming alpha subunit is sufficient for channel function, but the kinetics and voltage dependence of channel gating are in part modified by the beta subunits (Goldin et al, *Neuron* (2000), 28, 365–368). Electrophysiological recording, biochemical purification, and molecular cloning have identified ten different sodium channel alpha subunits and four beta subunits (Yu, F.H., *et al*, *Sci. STKE* (2004), 253; Yu, F.H., *et al*, *Neurosci.* (2003), 20:7577-85).

[0004] The sodium channel family of proteins has been extensively studied and shown to be involved in a number of vital body functions. Research in this area has identified variants of the alpha subunits that result in major changes in channel function and activities, which can ultimately lead to major pathophysiological conditions. The members of this family of proteins are denoted NaV1.1 to NaV1.9. However, until now, crystal structures of the binding site of sufficient resolution to permit study and design of inhibitor molecules were not available.

[0005] NaV1.7 is a tetrodotoxin-sensitive voltage-gated sodium channel encoded by the gene SCN9A. Human NaV1.7 was first cloned from neuroendocrine cells (Klugbauer, N., *et al*, 1995

EMBO J., 14 (6): 1084-90) and rat NaV1.7 was cloned from a pheochromocytoma PC12 cell line (Toledo-Aral, J. J., et al., *Proc. Natl.Acad. Sci. USA* (1997), 94:1527–1532) and from rat dorsal root ganglia (Sangameswaran, L., et al., (1997), *J. Biol. Chem.*, 272 (23): 14805-9). NaV1.7 is expressed primarily in the peripheral nervous system, especially nocieptors and olfactory neurons and sympathetic neurons. The inhibition, or blocking, of NaV1.7 has been shown to result in analgesic activity. Knockout of NaV1.7 expression in a subset of sensory neurons that are predominantly nociceptive results in resistance to inflammatory pain (Nassar, et al., op. cit.). Likewise, loss of function mutations in humans results in congenital indifference to pain (CIP), in which the individuals are resistant to both inflammatory and neuropathic pain (Cox, J.J., et al., *Nature* (2006);444:894-898; Goldberg, Y.P., et al., *Clin. Genet.* (2007);71:311-319). Conversely, gain of function mutations in NaV1.7 have been established in two human heritable pain conditions, primary erythromelalgia and familial rectal pain, (Yang, Y., et al., *J. Med. Genet.* (2004), 41(3):171-4). In addition, a single nucleotide polymorphism (R1150W) that has very subtle effects on the time- and voltage-dependence of channel gating has large effects on pain perception (Estacion, M., et al., 2009. *Ann Neurol.* 66: 862-6; Reimann, F., et al., *Proc. Natl. Acad Sci USA* (2010), 107: 5148-53). About 10% of the patients with a variety of pain conditions have the allele conferring greater sensitivity to pain and thus might be more likely to respond to block of NaV1.7. Because NaV1.7 is expressed in both sensory and sympathetic neurons, one might expect that enhanced pain perception would be accompanied by cardiovascular abnormalities such as hypertension, but no correlation has been reported. Thus, both the CIP mutations and SNP analysis suggest that human pain responses are more sensitive to changes in NaV1.7 currents than are perturbations of autonomic function.

[0006] Inhibitors of NaV1.7 can act through several mechanisms of action: pore binding such as via a local anesthetic, *e.g.*, TTX, STX; peptide voltage sensor domain (VSD) binders such as peptide toxins; and small molecule VSD4 binders, such as aryl- and acylsulfonamides as have previously been identified. Efforts to develop isoform selective NaV1.7 inhibitors have largely focused on VSD4 domain binders.

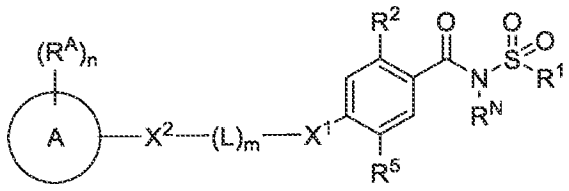
[0007] Sodium channel blockers have been shown to be useful in the treatment of pain, (see, e.g., Wood, J.N., et al, *J. Neurobiol.* (2004), 61(1), 55-71. Genetic and functional studies have provided evidence to support that activity of NaV1.7 as a major contributor to pain signalling in mammals. (See Hajj, et al. *Nature Reviews Neuroscience*; 2013, vol 14, 49-62; and Lee, et al. *Cell*, 2014, vol 157; 1-12). Presently, there are a limited number of effective sodium channel blockers for the treatment of pain with a minimum of adverse side effects which are currently in

the clinic. Thus there remains a need for selective voltage-gated sodium channel modulators (e.g., modulators of NaV1.7) that are useful for the treatment of pain. However, efforts to improve upon existing chemical matter via structure-based drug design have been complicated by the recalcitrance of the channel toward X-ray crystallographic co-structure determination.

SUMMARY

[0008] In one aspect the present invention provides novel compounds having sodium channel blocking activity that are useful for the treatment of pain.

[0009] In a first embodiment (Embodiment 1; abbreviated as "E1") the invention provides a compound of Formula I:



(I)

and pharmaceutically acceptable salts thereof, wherein in Formula I, the variables have the following values.

[0010] R^1 is selected from a first set of moieties consisting of C_{1-8}alkyl, C_{3-12}cycloalkyl, C-linked C_{2-11}heterocycloalkyl, C_{3-12}carbocycle, aryl, heteroaryl, and $-NR^{1A}R^{1B}$, wherein:

R^{1A} and R^{1B} are selected from H, C_{1-8}alkyl, C_{3-8}cycloalkyl, C_{1-8}haloalkyl, or R^{1A} and R^{1B} together with the nitrogen atom to which they are both bonded form a 3 to 10 membered heterocyclic group;

any of the first set of moieties, R^{1A}, or R^{1B}, is optionally substituted with one or more substituents selected from a second set of moieties consisting of:

C_{1-8}alkyl, C_{2-8}alkenyl, C_{3-8}cycloalkyl, C_{1-8}haloalkyl, aryl, (aryl)C_{1-8}alkyl, heteroaryl, (heteroaryl)C_{1-8}alkyl, C_{2-11}heterocycloalkyl, (C_{2-11}heterocycloalkyl)C_{1-8}alkyl, F, Cl, Br, I, –OH, –CN, $–NO_2$, =O, aminocarbonyl, $–X^{R1}NR^{R1a}R^{R1b}$, $–X^{R1}OR^{R1a}$, and $–X^{R1}SR^{R1a}$, wherein:

X^{R1} is selected from the group consisting of C(=O), C_{1-4} alkylene, C_{1-4}heteroalkylene, C_{2-4}alkenylene and C_{2-4} alkynylene, or is absent; and

R^{R1a} and R^{R1b} are independently selected from a third set of moieties consisting of: H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{1-8}haloalkyl, C_{3-8}cycloalkyl,

C_{3-12}carbocycle, (C_{3-8} cycloalkyl)C_{1-8} alkyl, aryl, (aryl)C_{1-8}alkyl, heteroaryl, (heteroaryl)C_{1-8}alkyl, C_{2-11}heterocycloalkyl, and (C_{2-11}heterocycloalkyl)C_{1-8}alkyl,

or R^{R1a} and R^{R1b} together with the nitrogen atom to which they are both bonded form a 3 to 10 membered heterocyclic group;

and

wherein any of the second set of moieties, R^{R1a}, or R^{R1b}, where present, are each optionally substituted by one or more groups independently selected from: C_{1-8} alkyl, C_{1-8}haloalkyl, F, Cl, Br, I, -OH, -CN, aryl, C_{1-8}haloalkyl-substituted aryl, C_{1-8}alkoxy, C_{1-8}alkanoyl, C_{1-8}alkoxycarbonyl, C_{3-8}cycloalkyl, C_{2-11}heterocycloalkyl, amino, (C_{1-3}alkyl)amino, di(C_{1-3}alkyl)amino, C_{1-3}alkylamido, C_{1-3}alkylcarboxy, and -NO_2;

[0011] R^N is hydrogen, C_{1-4} alkyl, or C_{1-4}haloalkyl;

[0012] R^2 is selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl and C_{1-8} alkoxy;

[0013] R^5 is selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{2-11} heterocycloalkyl, phenyl and 5-6 membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O and S, wherein said 5-6 membered heteroaryl, C_{1-8} alkyl, C_{3-8} cycloalkyl or C_{2-11} heterocycloalkyl is further optionally substituted with from 1 to 3 substituents selected from F, Cl, Br, I, -OH , =O, C_{3-6} cycloalkyl, -CN, C_{1-4} alkyl, -C_{1-4} alkyl-O-C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} alkoxy;

[0014] L is a linker selected from the group consisting of C_{1-4} alkylene, C_{2-4} alkenylene, C_{2-4} alkynylene, and C_{1-4} heteroalkylene, wherein L is optionally substituted with from 1 to 3 substituents selected from the group consisting of =O, -OH, -OCH_2-phenyl, C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} acyl;

[0015] m is 0 or 1;

[0016] X^1 and X^2 are each independently selected from the group consisting of, –O–, –S(O) –, –$S(O)_2$– and –$N(R^X)$– wherein R^X is H, C_{1-8} alkyl, C_{1-8} acyl and -$S(O)_2$(C_{1-8} alkyl), or is absent, and wherein if m is 0 then at least one of X^1 or X^2 is absent;

[0017] n is an integer from 0 to 5;

[0018] **A** is selected from the group consisting of: hydrogen, C_{1-8}alkyl, C_{1-8}haloalkyl, C_{3-12} cycloalkyl, and aryl, and wherein if A is hydrogen then n is 0;

[0019] each $\mathbf{R^A}$ is independently selected from the group consisting of C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, =O, heteroaryl, $-(X^{RA})_{0-1}NR^{A1}R^{A2}$, $-(X^{RA})_{0-1}OR^{A1}$, $-(X^{RA})_{0-1}SR^{A1}$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)OR^{A3}$, $-(X^{RA})_{0-1}OC(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}C(=O)N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})C(=O)R^{A2}$, $-(X^{RA})_{0-1}C(=O)OR^{A1}$, $-(X^{RA})_{0-1}OC(=O)R^{A1}$, $-P(=O)(OR^{A1})(OR^{A2})$, $-(X^{RA})_{0-1}S(O)_{1-2}R^{A3}$, $-(X^{RA})_{0-1}S(O)_{1-2}N(R^{A1})(R^{A2})$, $-(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}N(R^{A1})(R^{A2})$ and $-(X^{RA})_{0-1}N(R^{A1})S(O)_{1-2}(R^{A3})$, wherein X^{RA} is selected from the group consisting of C_{1-4} alkylene, C_{1-4} heteroalkylene, C_{2-4} alkenylene and C_{2-4} alkynylene; wherein R^{A1} and R^{A2} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, heteroaryl, and C_{2-11} heterocycloalkyl; R^{A3} is selected from the group consisting of C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, tetrahydronapthalene, phenyl, benzyl, heteroaryl, and C_{2-11} heterocycloalkyl; wherein if A is a monocyclic C_{3-12} carbocycloalkyl or monocyclic C_{2-11} heterocycloalkyl, then any two R^A substituents attached to adjacent atoms on the A ring are optionally combined to form a benzene or a 5 to 6 membered heteroaryl ring; and wherein the aliphatic and aromatic portions of a R^A subsitutent is optionally substituted with from 1 to 5 R^{RA} substitutents selected from, F, Cl, Br, I, $-NH_2$, -OH, -CN, $-NO_2$, =O, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} (halo)alkyl-C(=O)-, C_{1-4} (halo)alkyl-$S(O)_{0-2}$-, C_{1-4} (halo)alkyl-C(=O)N(H)-, C_{1-4} (halo)alkyl-N(H)-C(=O)-, ((halo)alkyl)$_2$N-C(=O)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, C_{1-4} (halo)alkyl-OC(=O)N(H)-, (halo)alkyl-N(H)-C(=O)O-, ((halo)alkyl)$_2$N-C(=O)O-, C_{1-4} alkylamino, C_{1-4} dialkylamino, C_{3-6} cycloalkyl, C_{3-6} cycloalkoxy, C_{2-5} heterocycloalkoxy, tetrahydronaphthalene and phenyl wherein phenyl is optionally substituted with 1-3 fluoro, chloro, bromo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkoxy , C_{1-6} alkylamino, C_{1-6} or dialkylamino.

[0020] In another embodiment E2, the invention provides a compound or pharmaceutically acceptable salt of E1, wherein **n** is 0.

[0021] In another embodiment E3, the invention provides a compound or pharmaceutically acceptable salt of E1 or E2, wherein **A** is C_{3-6}cycloalkyl.

[0022] In another embodiment E4, the invention provides a compound or pharmaceutically acceptable salt of E1 or E2 wherein **A** is cyclopentyl.

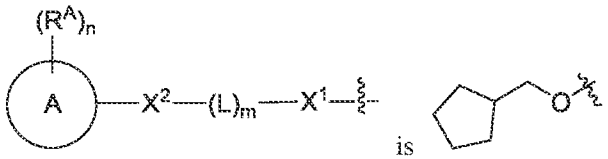
[0100] In another embodiment E5, the invention provides a compound or pharmaceutically acceptable salt of E1, E2, E3, or E4, wherein X^1 is -O-.

[0023] In another embodiment E6, the invention provides a compound or pharmaceutically acceptable salt of E1, E2, E3, E4, or E5, wherein $\mathbf{X^2}$ is absent.

[0024] In another embodiment E7, the invention provides a compound or pharmaceutically acceptable salt of E1, E2, E3, E4, E5, or E6, wherein **L** is C_{1-4} alkylene.

[0025] In another embodiment E8, the invention provides a compound or pharmaceutically acceptable salt of E1, E2, E3, E4, E5, or E6, wherein **L** is methylene.

[0026] In another embodiment E9, the invention provides a compound or pharmaceutically acceptable salt of E1, wherein the group



is .

[0027] In another embodiment E10, the invention provides a compound or pharmaceutically acceptable salt of E1, E2, E3, E4, E5, E6, E7, E8, or E9, wherein $\mathbf{R^2}$ is H or F.

[0028] In another embodiment E11, the invention provides a compound or pharmaceutically acceptable salt of E1, E2, E3, E4, E5, E6, E7, E8, or E9, wherein $\mathbf{R^2}$ is F.

[0029] In another embodiment E12, the invention provides a compound or pharmaceutically acceptable salt of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10 or E11, wherein $\mathbf{R^5}$ is selected from the group consisting of H, F, Cl, C_{1-8} alkyl, C_{1-8} alkoxy, and C_{3-8} cycloalkyl.

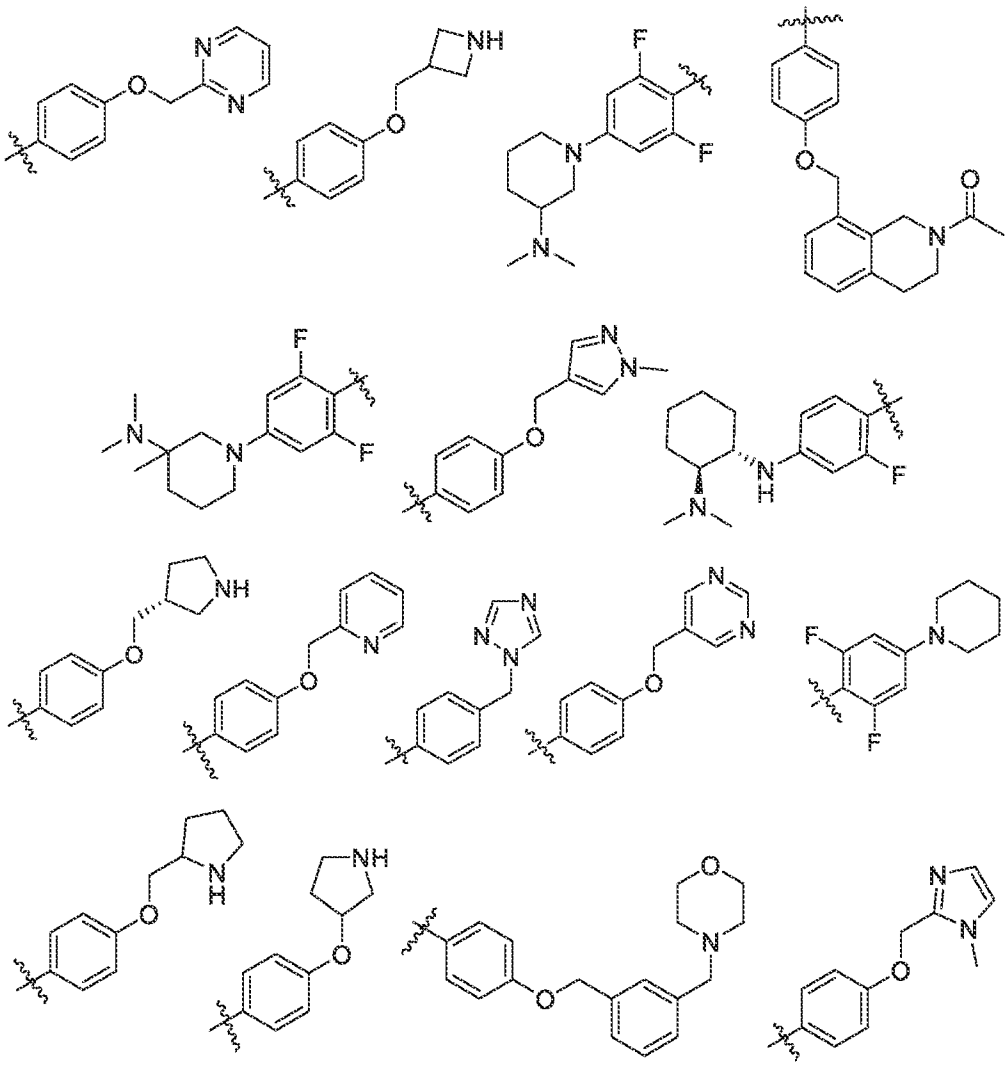
[0030] In another embodiment E13, the invention provides a compound or pharmaceutically acceptable salt of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10 or E11, wherein $\mathbf{R^5}$ is selected from the group consisting of H, F, Cl, ethyl, isopropyl, cyclopropyl, and methoxy.

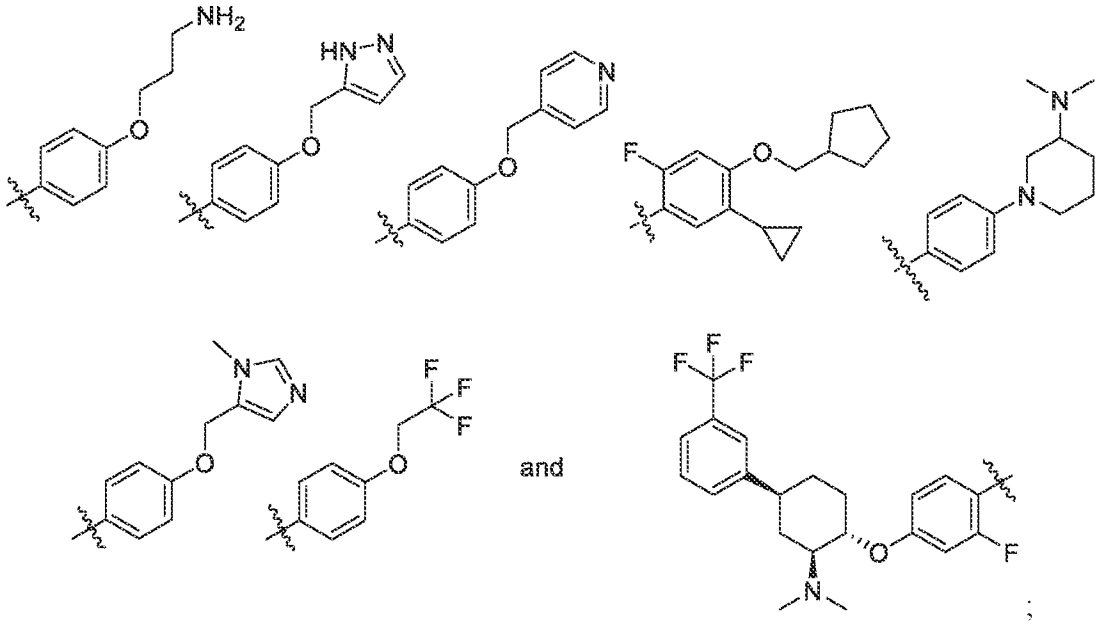
[0031] In another embodiment E14, the invention provides a compound or pharmaceutically acceptable salt of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10 or E11, wherein $\mathbf{R^5}$ is selected from the group consisting of methyl, Cl and cyclopropyl.

[0032] In another embodiment E15, the invention provides a compound or pharmaceutically acceptable salt of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10 or E11, wherein $\mathbf{R^5}$ is Cl.

[0033] In another embodiment E16, the invention provides a compound or pharmaceutically acceptable salt of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, or E15, wherein: $\mathbf{R^1}$ is aryl that is optionally substituted with from 1 or 2 R^{R1} substituents independently selected from the group consisting of C_{1-3}alkyl, trifluoromethyl, C_{3-5} cycloalkyl, F, Cl, Br, I, -OH, -CN, -$(X^{1R})_{0-1}NR^{R1a}R^{R1b}$, -$(X^{1R})_{0-1}OR^{R1a}$, wherein X^{1R} is C_{1-3} alkylene; and wherein R^{R1a} and R^{R1b} are independently selected from the group consisting of hydrogen, C_{1-3} alkyl, trifluoromethyl, C_{3-6} cycloalkyl, phenyl, and benzyl, wherein any phenyl, and benzyl of R^{R1a} and R^{R1b} is optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of F, Cl, aminomethyl, C_{1-3} alkyl, C_{1-3} alkoxy, and dimethylamino;

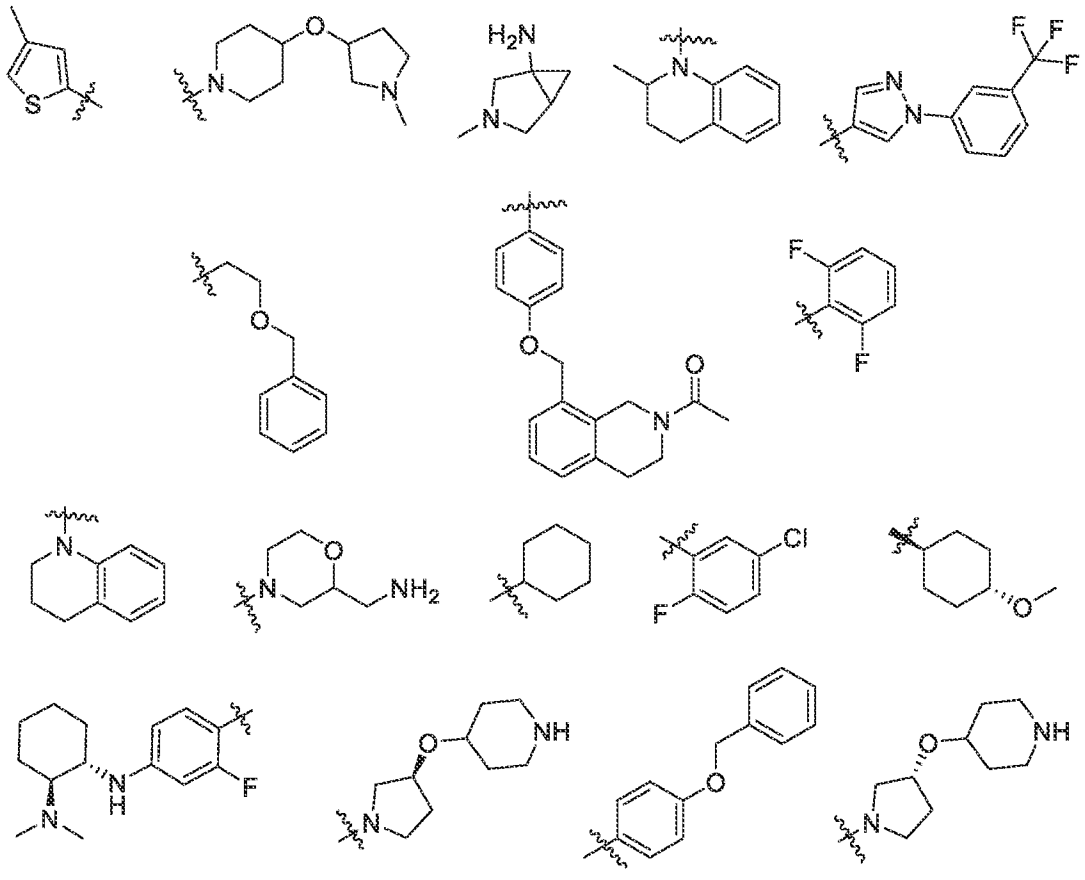
or $\mathbf{R^1}$ is selected from the group consisting of:

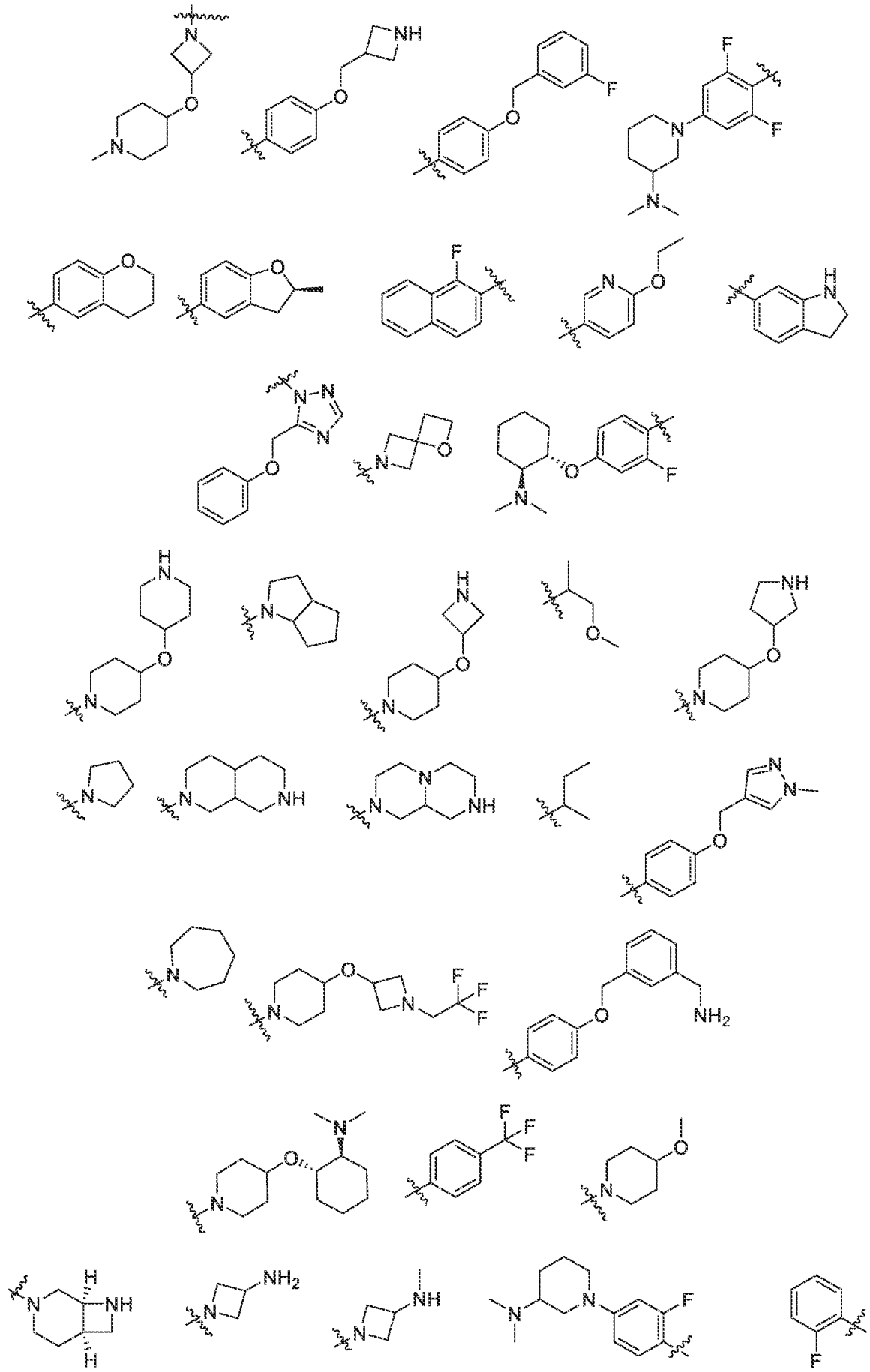


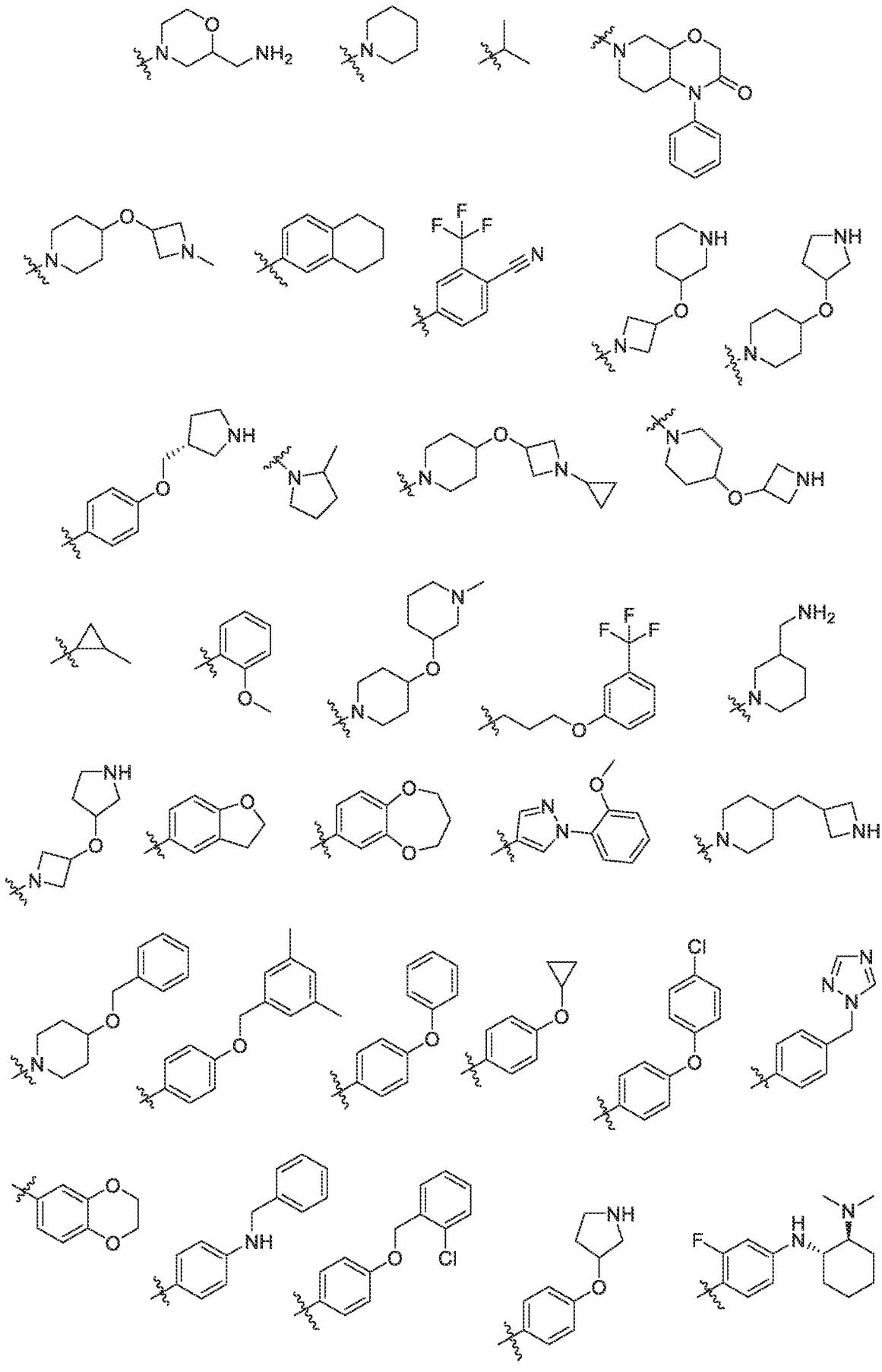


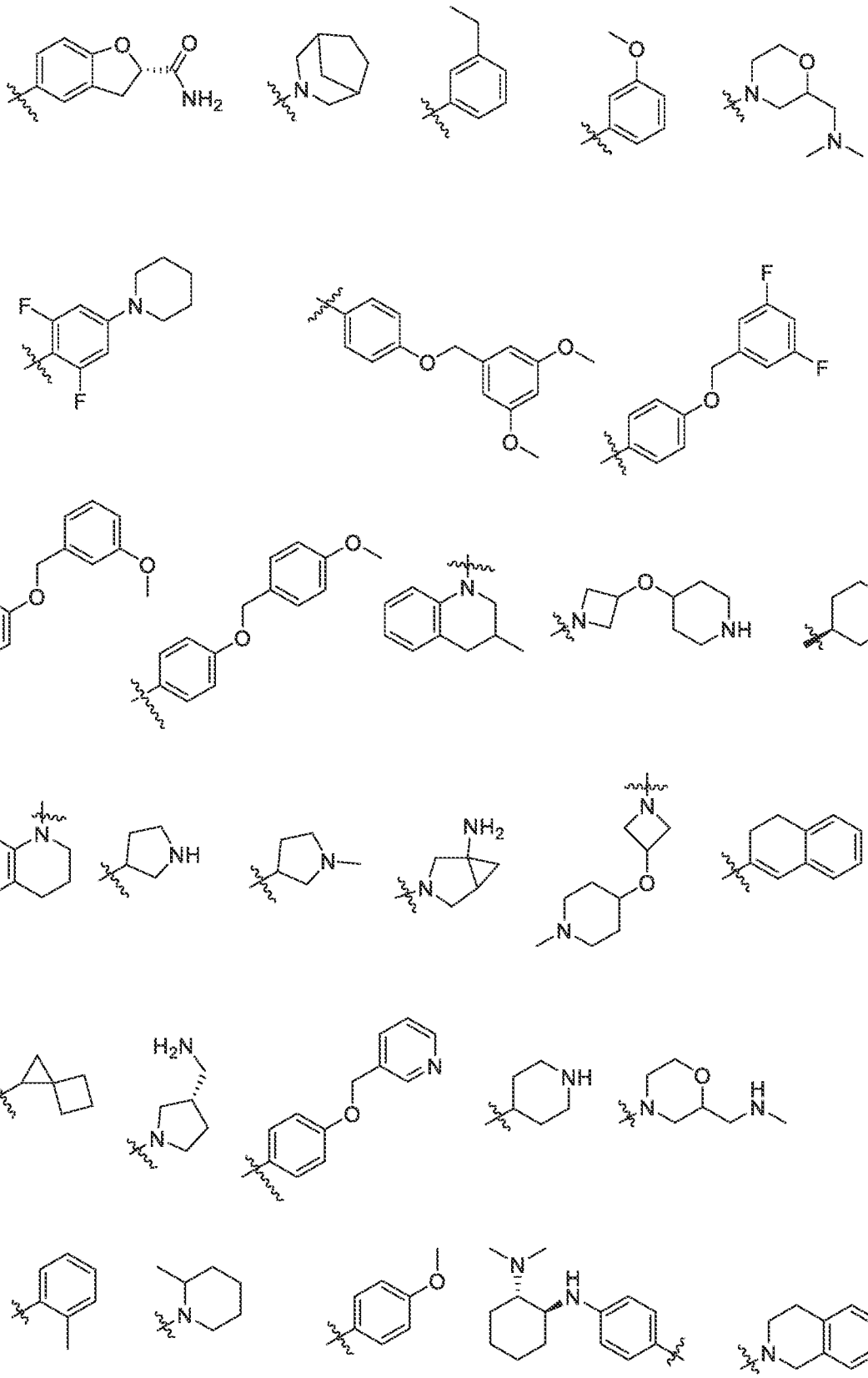
provided $\mathbf{R^1}$ is not 3-chloro-4-cyanophenyl.

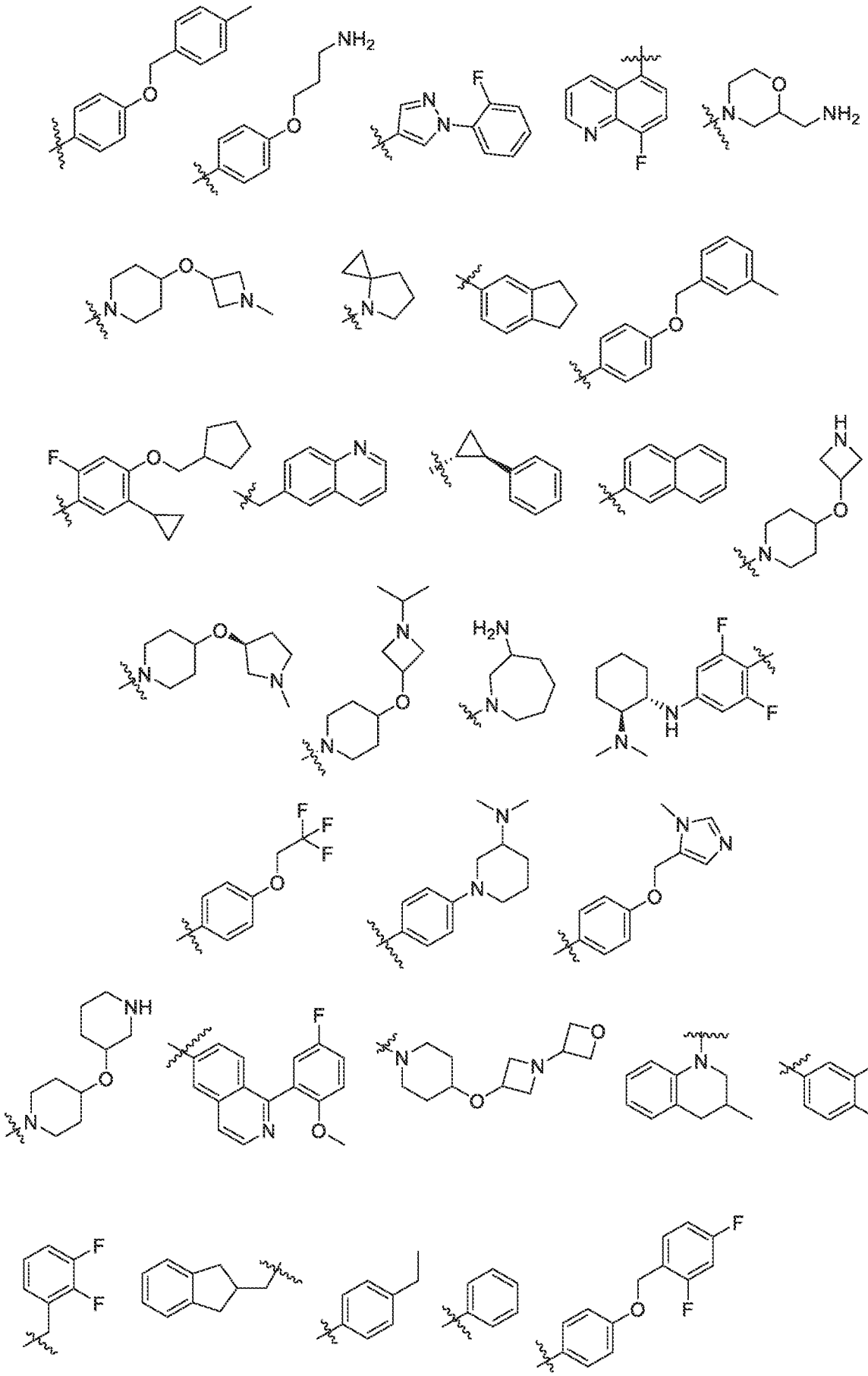
[0034] In another embodiment E17, the invention provides a compound or pharmaceutically acceptable salt of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, or E15, wherein $\mathbf{R^1}$ is selected from the group consisting of any instance of R^1 as found in compounds of the Examples herein, and additionally or including the following groups:

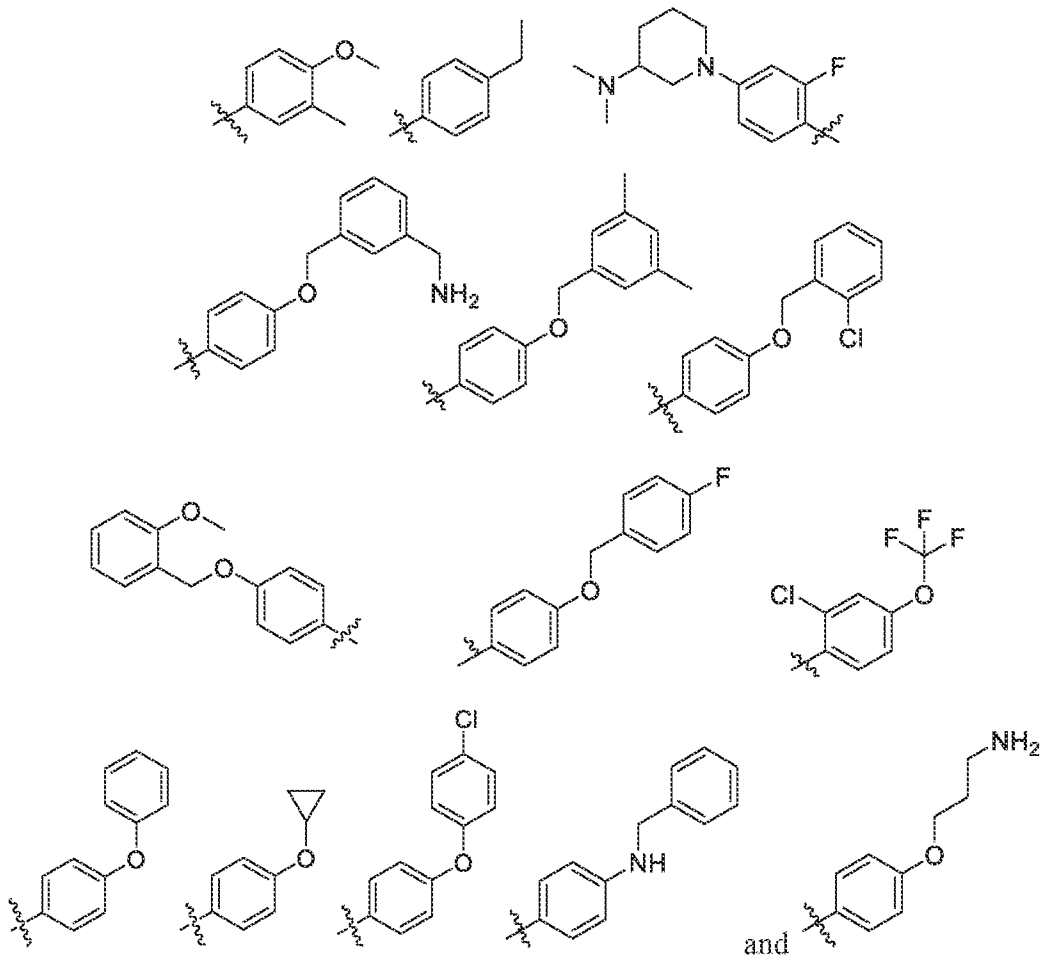












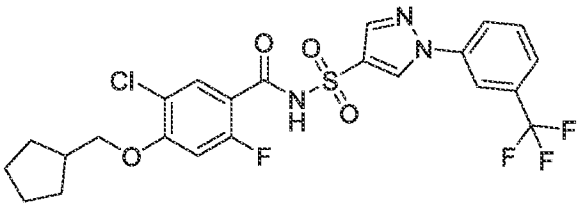
[0035] In another embodiment E18, the invention provides a compound or pharmaceutically acceptable salt of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, E15, E16, or E17 wherein $\mathbf{R^N}$ is hydrogen.

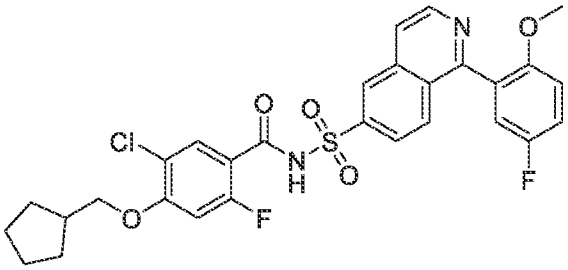
[0036] In another embodiment E19, the invention provides a compound or pharmaceutically acceptable salt of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, E15, E16, E17, or E18 wherein each $\mathbf{R^A}$ is independently selected from the group consisting of C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, and =O.

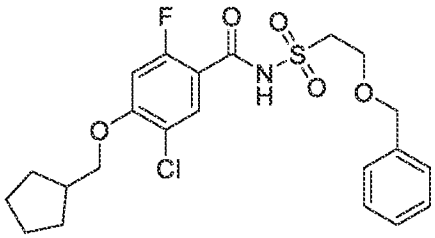
[0037] In another embodiment, E20, the invention provides a compound or pharmaceutically acceptable salt of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, E15, E16, E17, or E18, wherein each $\mathbf{R^A}$ is independently selected from the group consisting of C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, and =O.

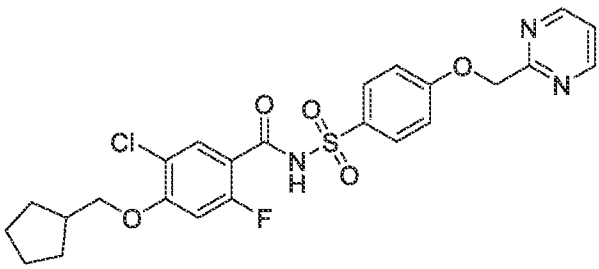
[0038] In another embodiment E21, the invention provides a compound or pharmaceutically acceptable salt of E1 selected from the group consisting of the compounds described in the individual Examples herein, as well as the following exemplary compounds. Compounds in the

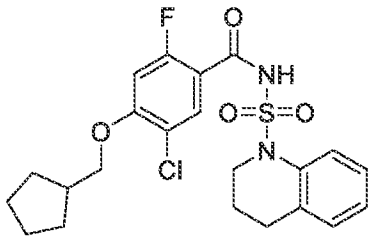
following group may also be found individually characterized in the Examples herein. Compounds characterized in the Examples herein that are not specifically enumerated in the following list are also considered to be part of the invention. It is intended that, where specific chirality is not designated at a given chiral center, then either enantiomer or diastereomer of the depicted compound is encompassed.

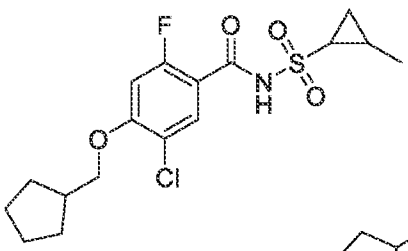


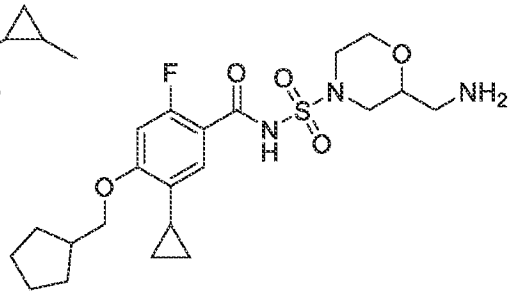


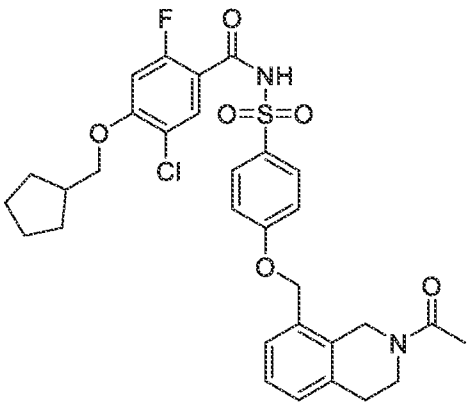


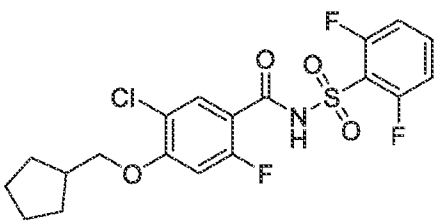


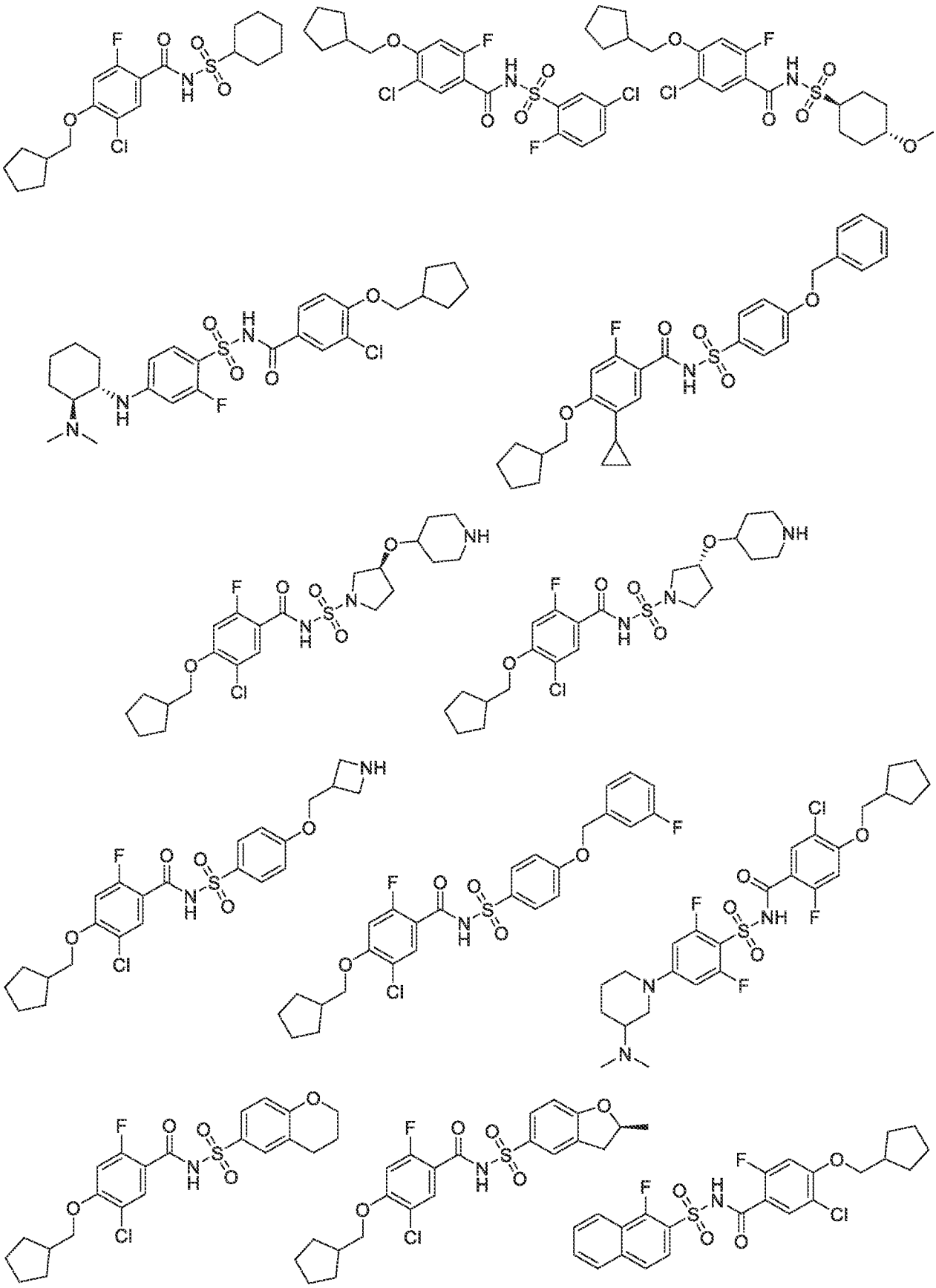


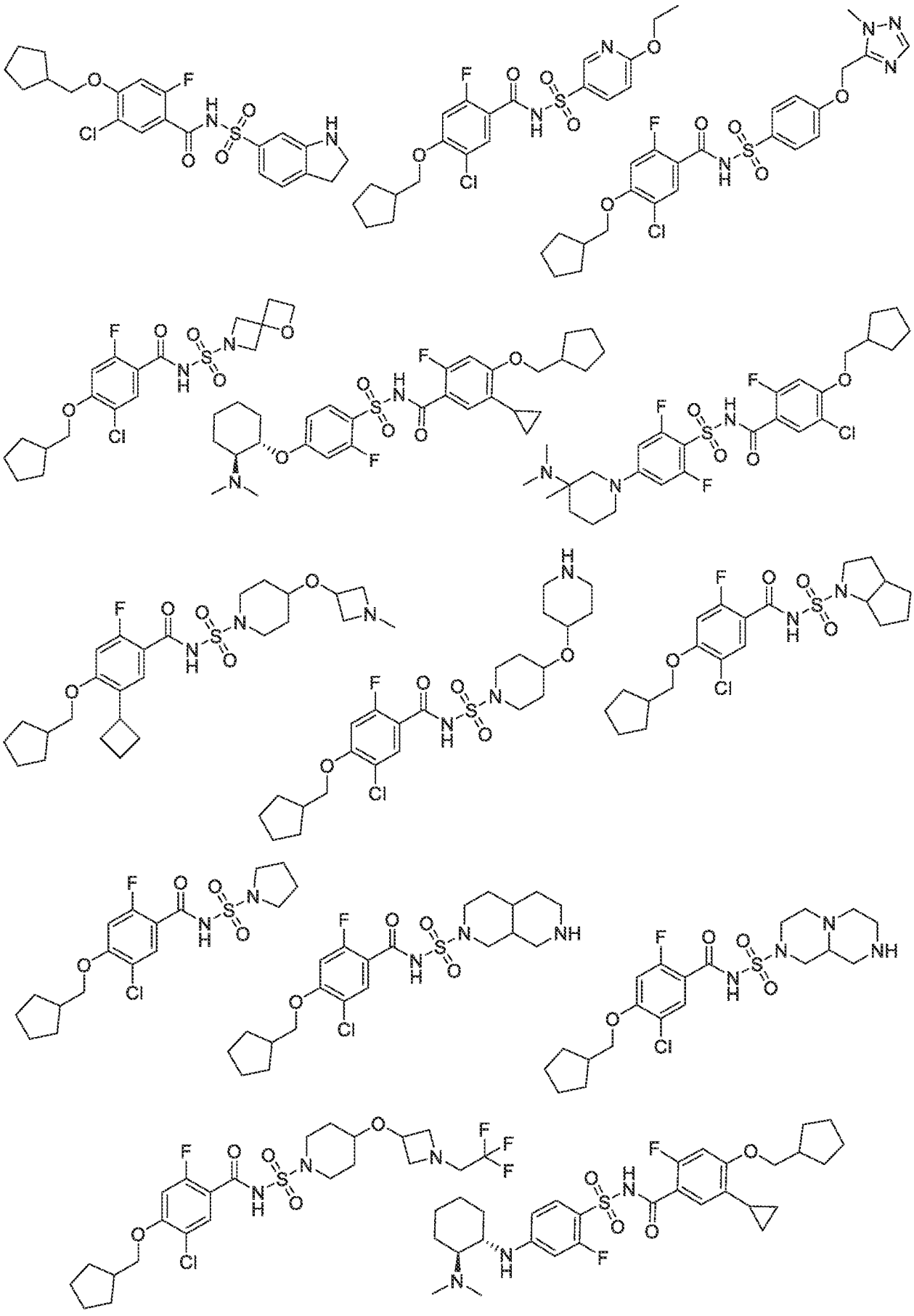


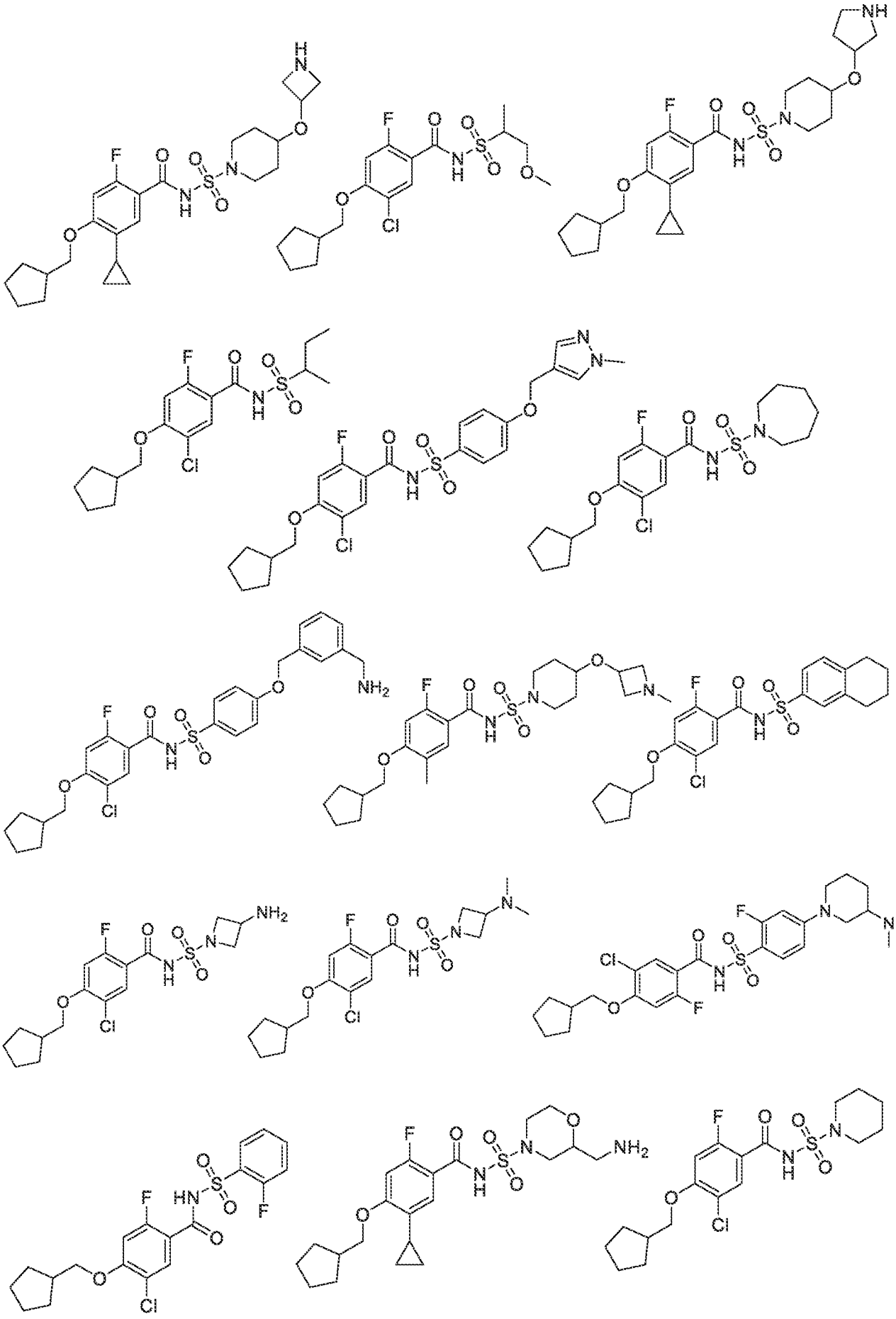


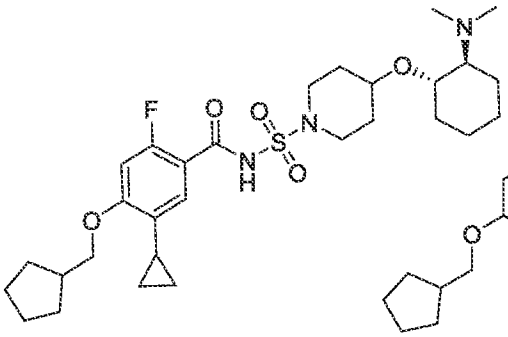


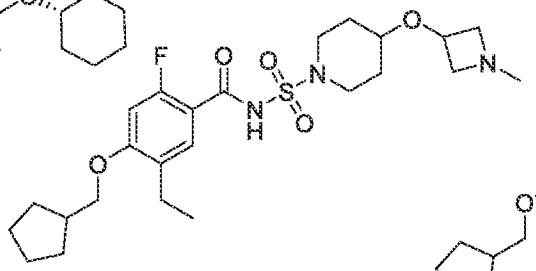


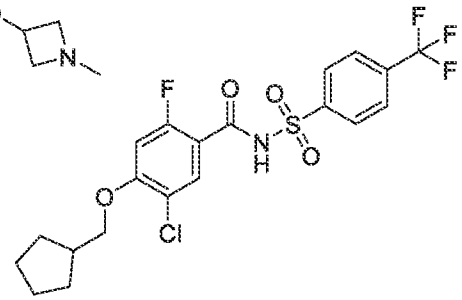


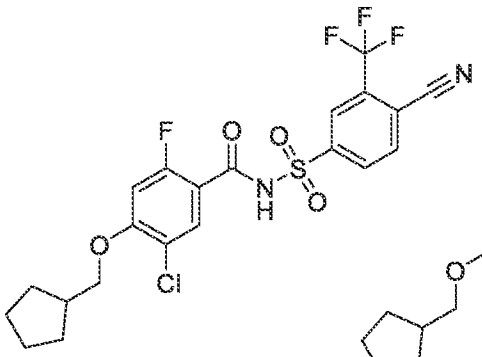


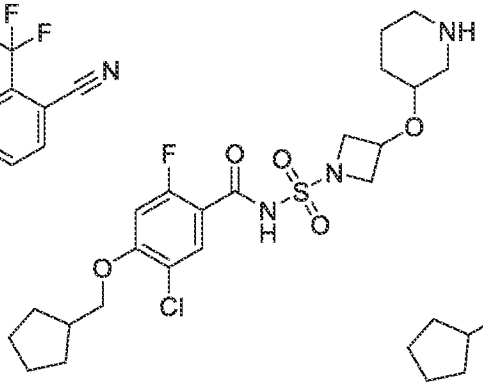


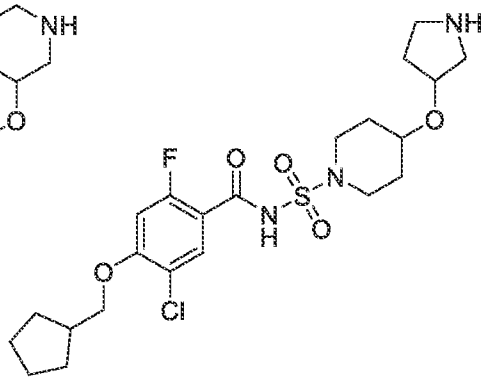


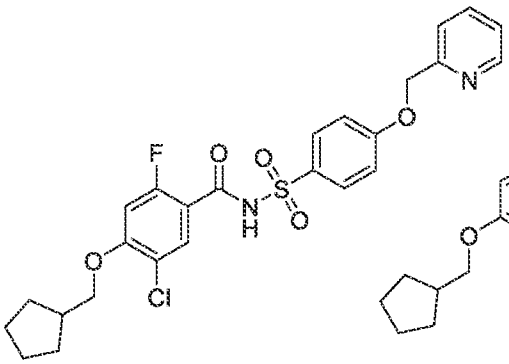


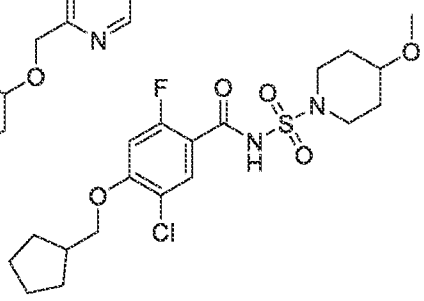


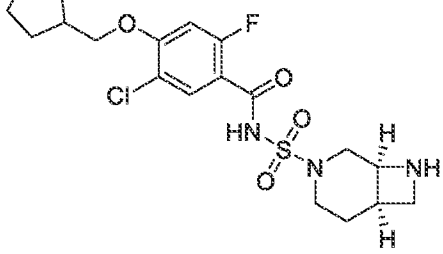


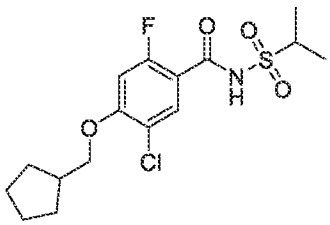


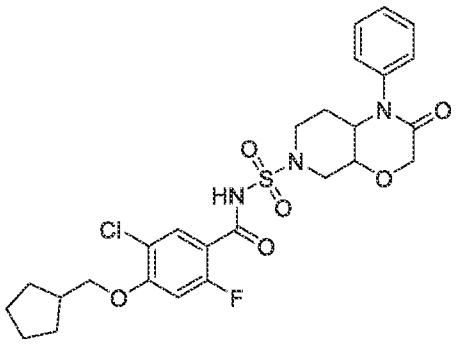


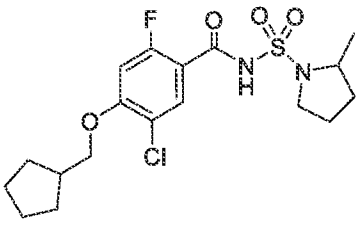


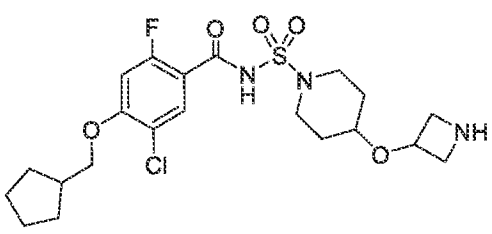


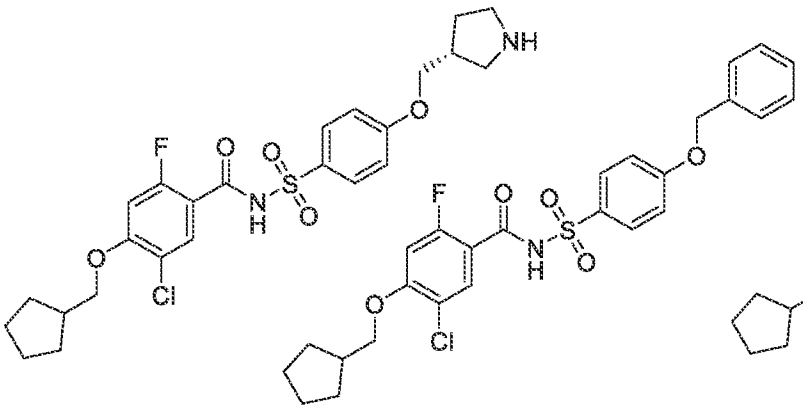


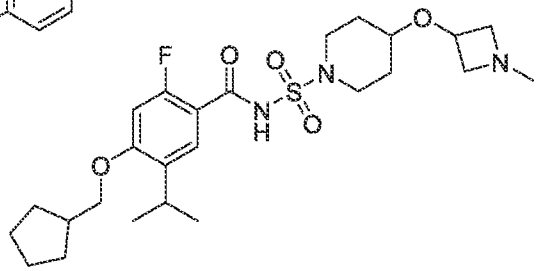


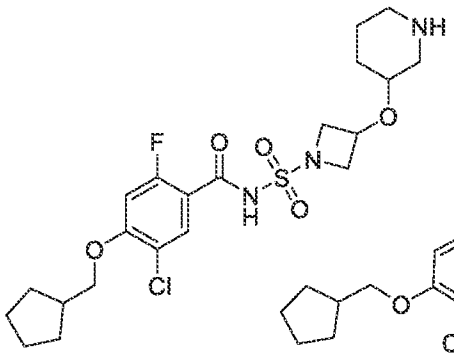


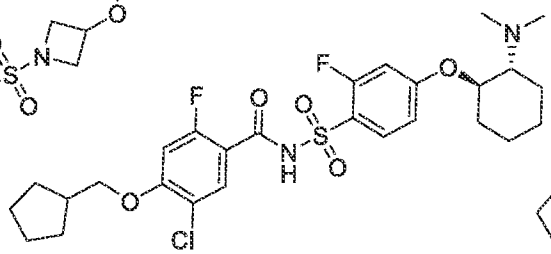


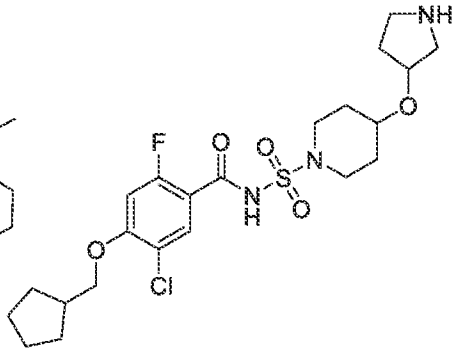


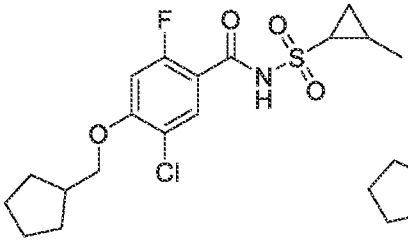


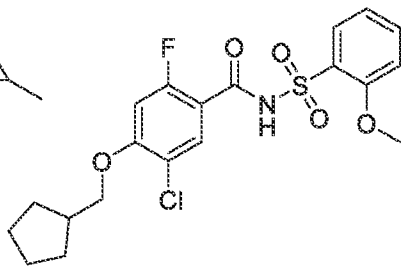


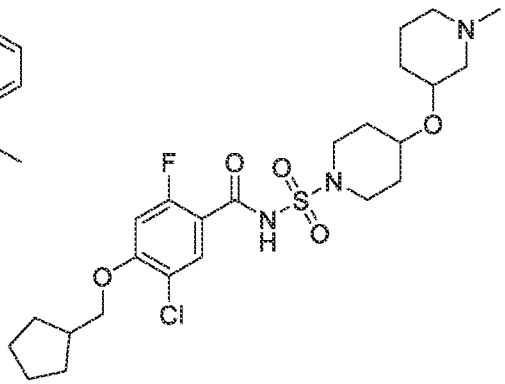


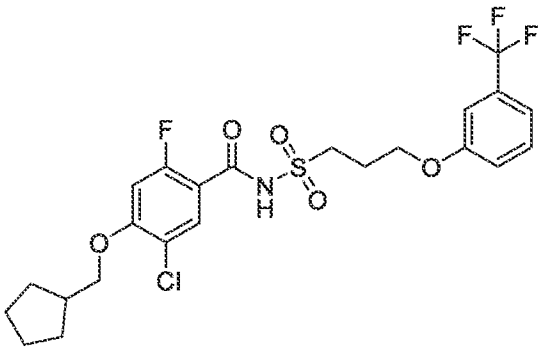


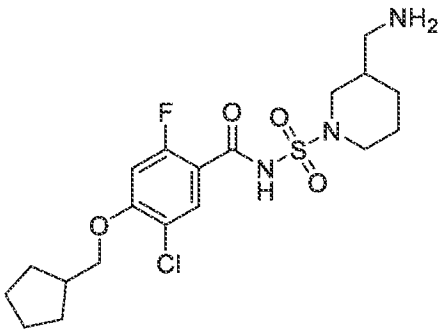


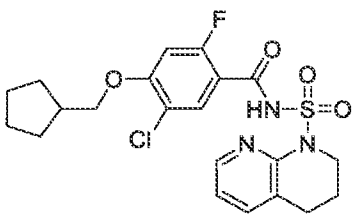


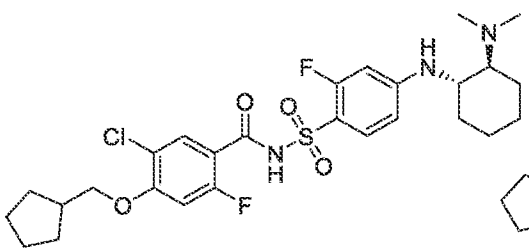


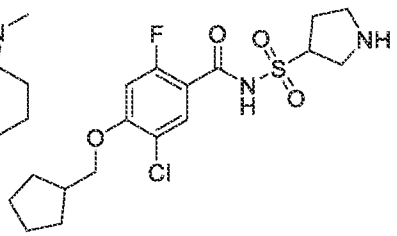


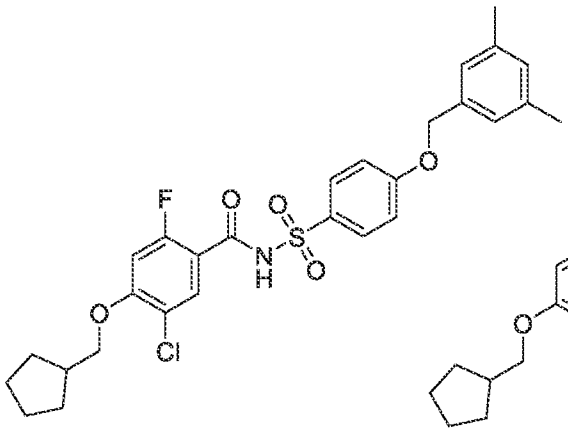


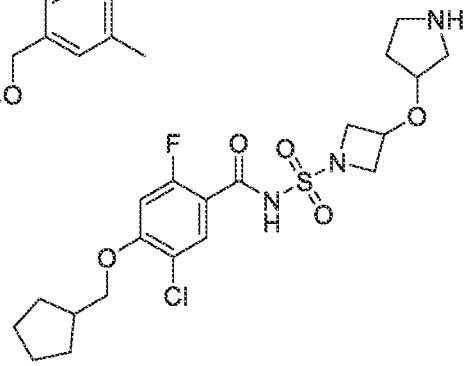


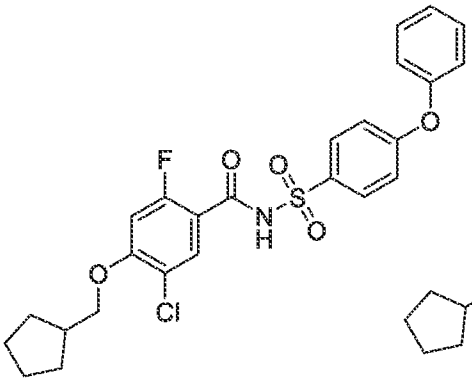


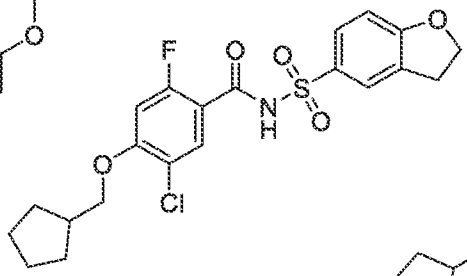


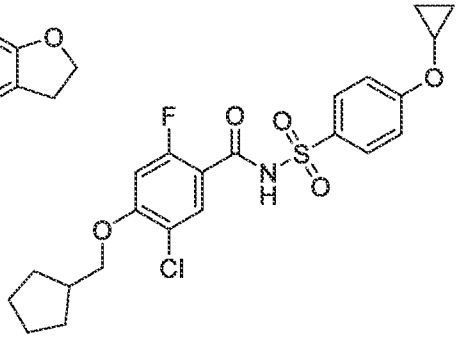


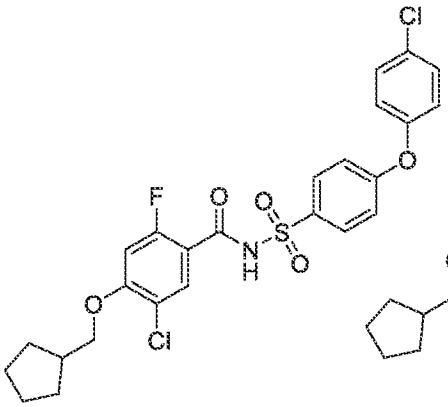


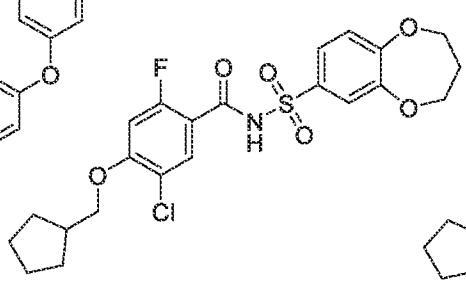


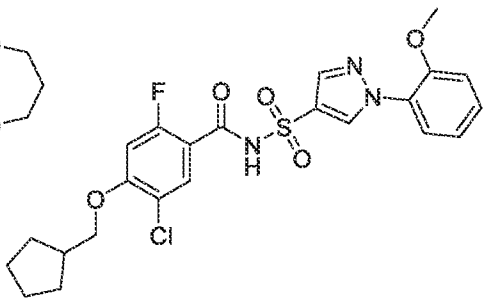


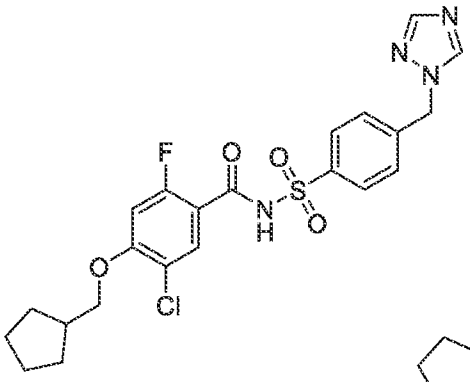


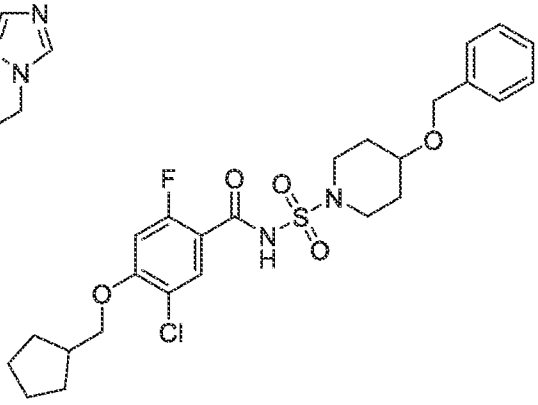


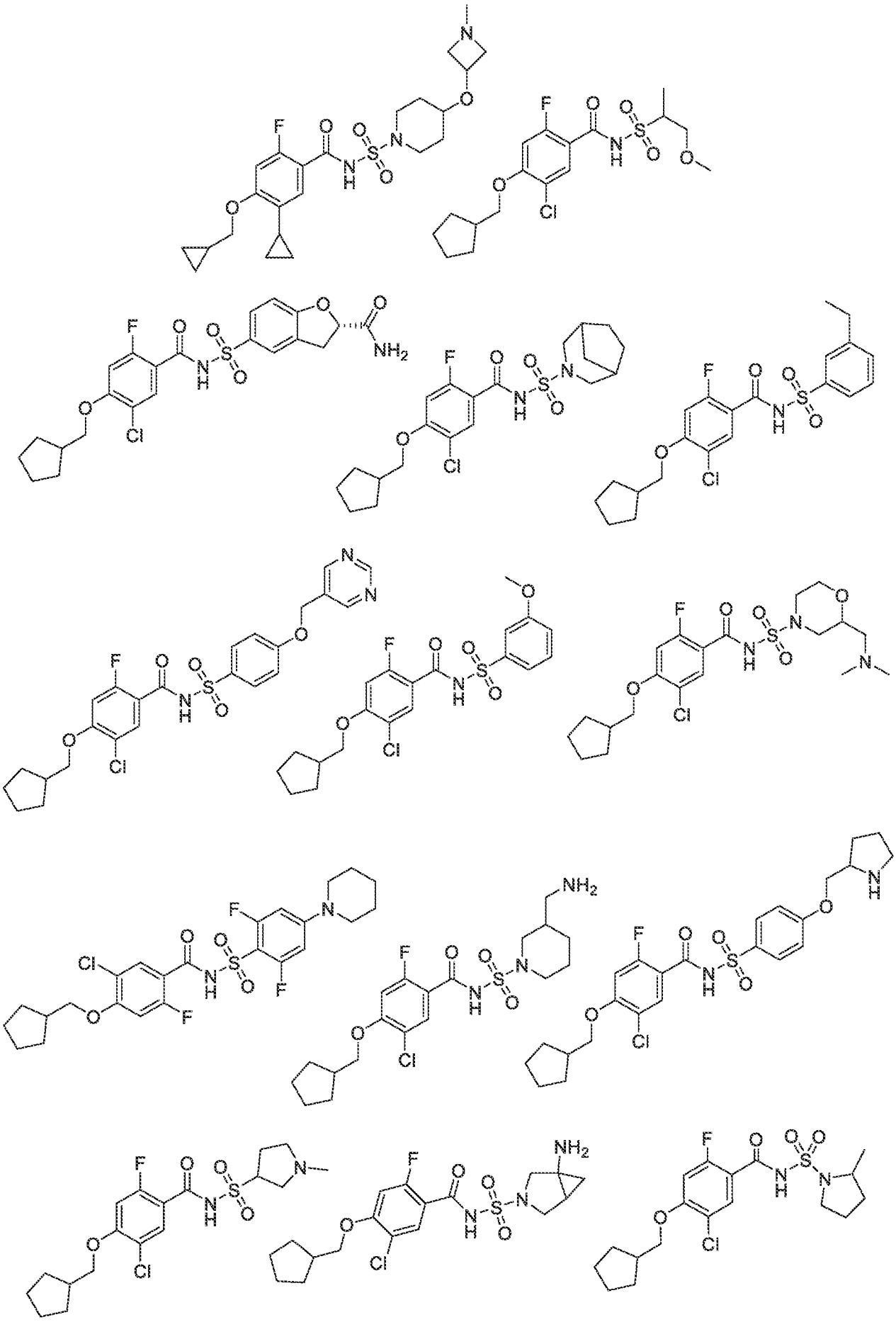


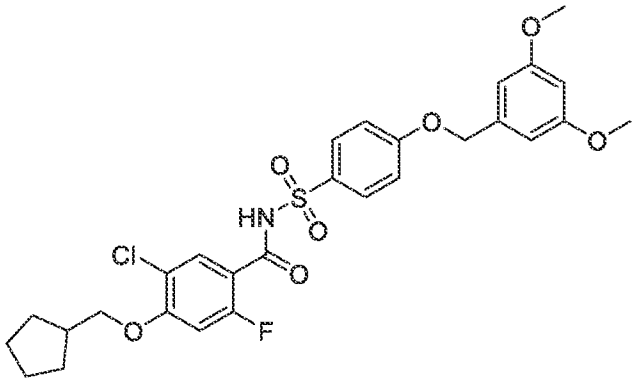


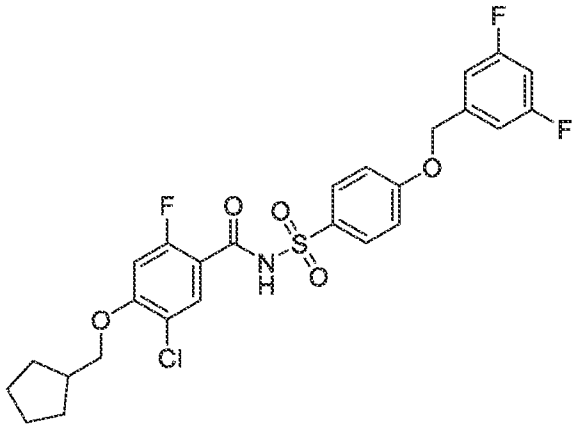


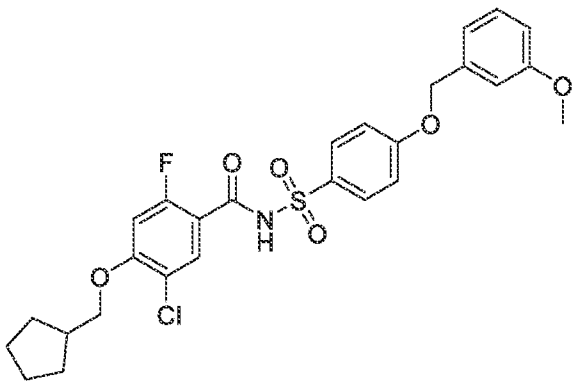


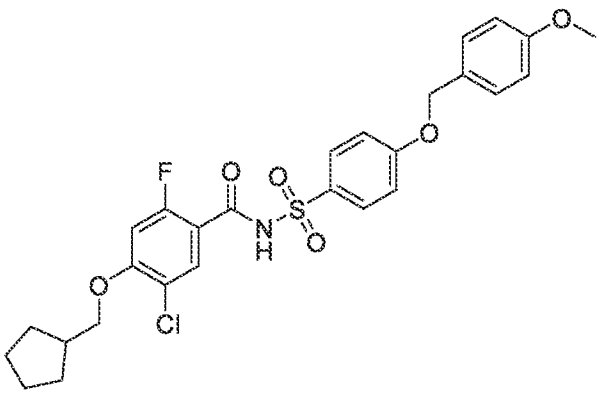


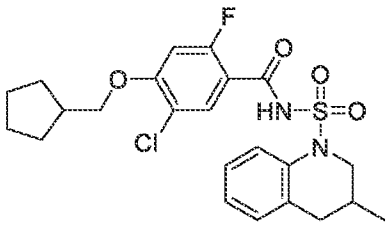


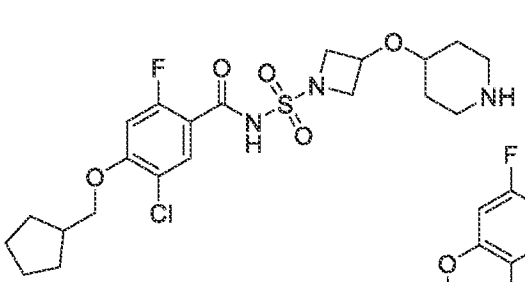


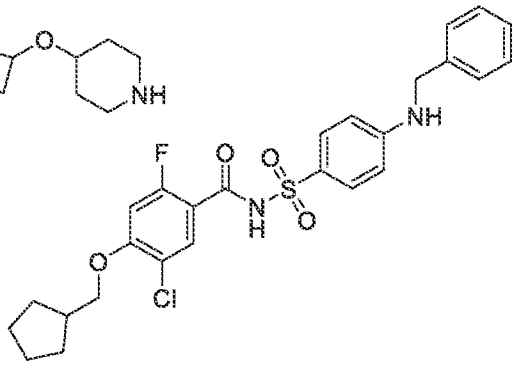


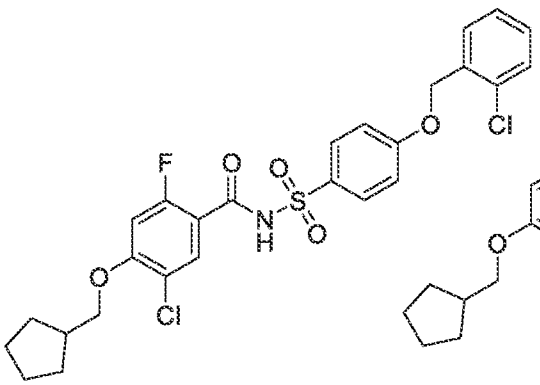


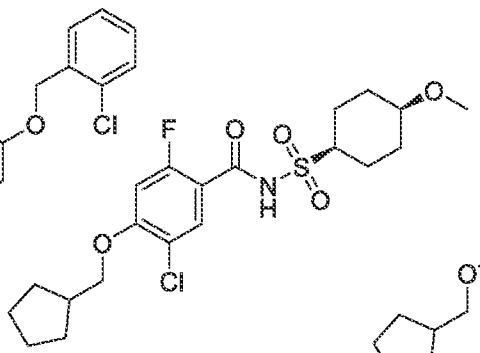


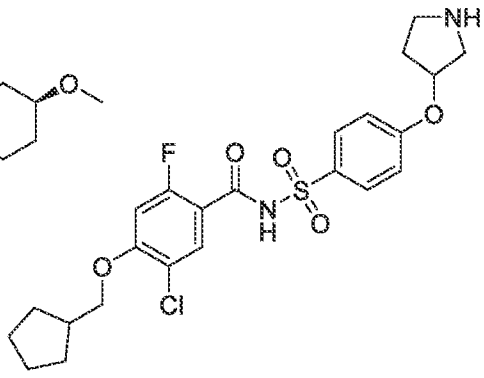


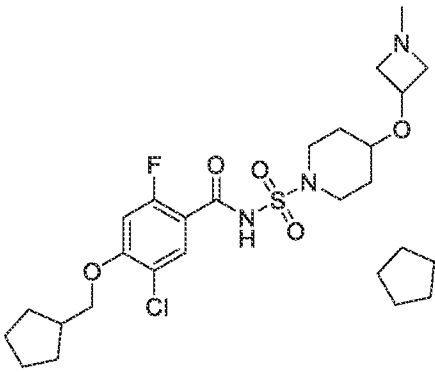


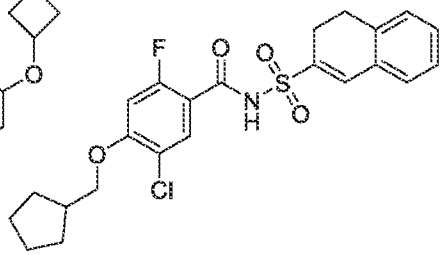


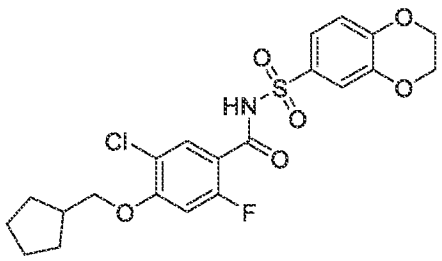


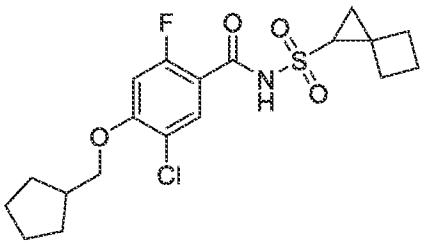


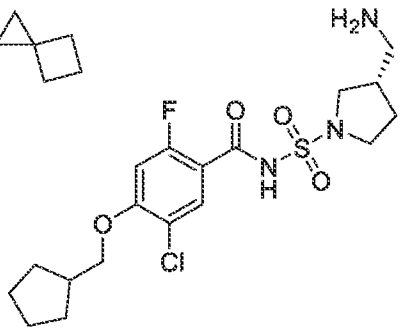


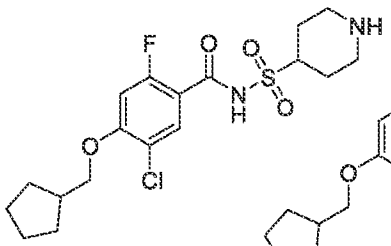


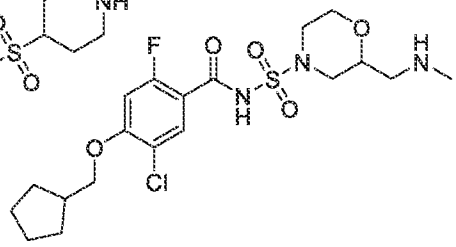


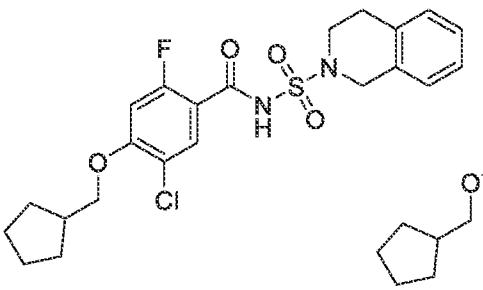


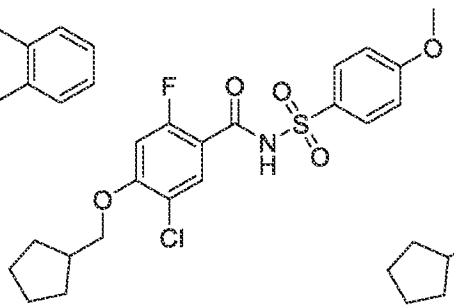


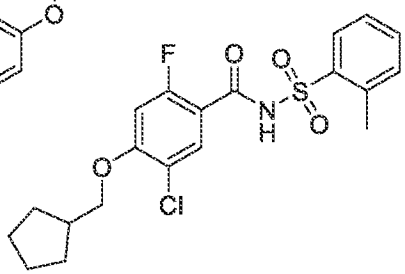


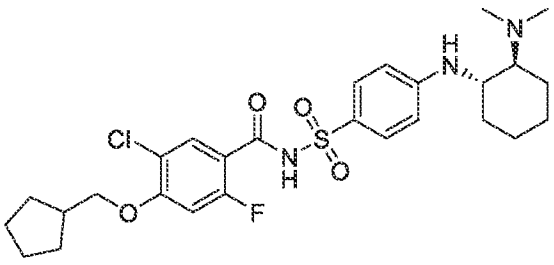


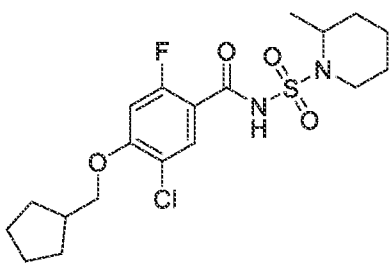


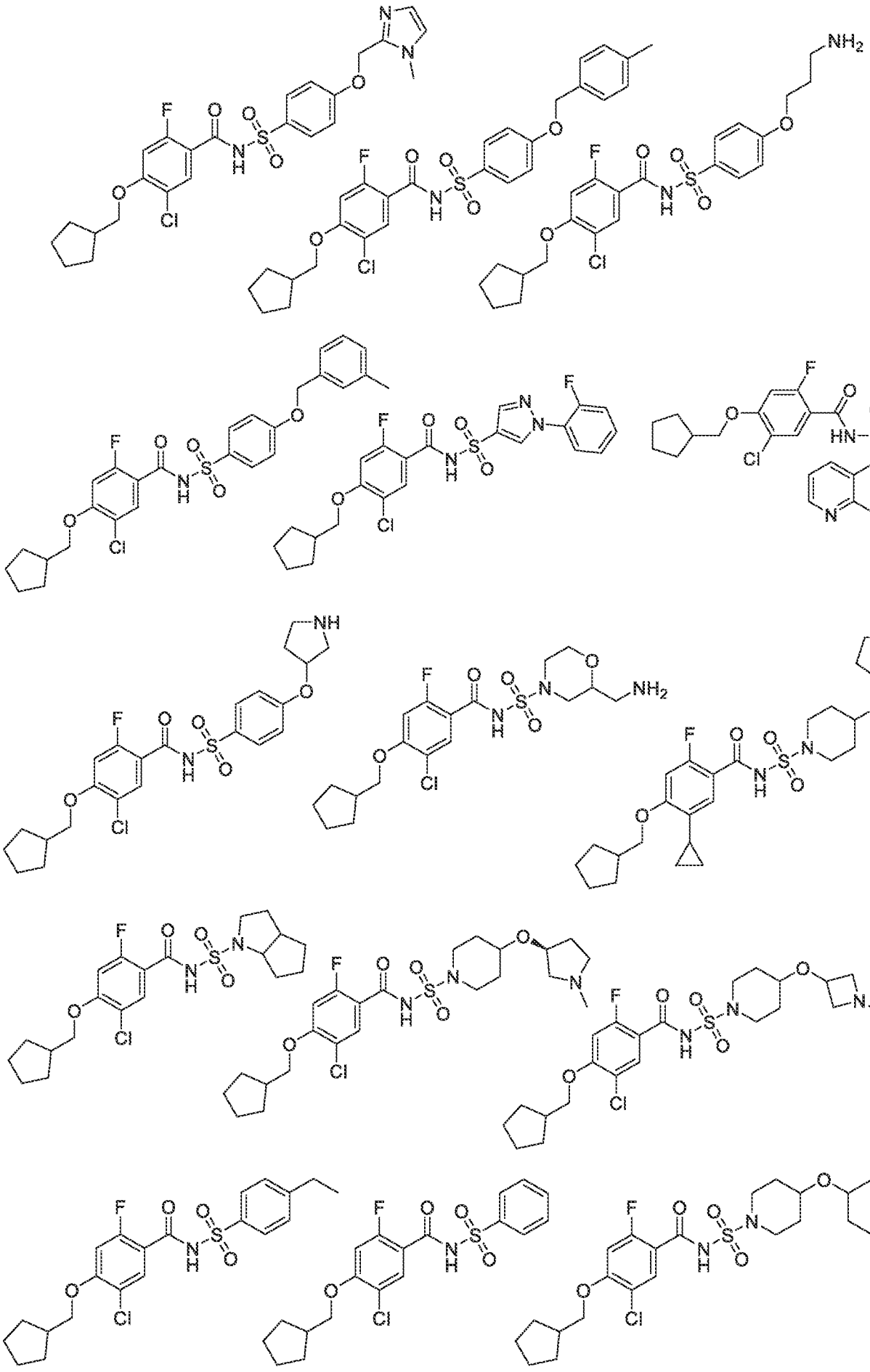


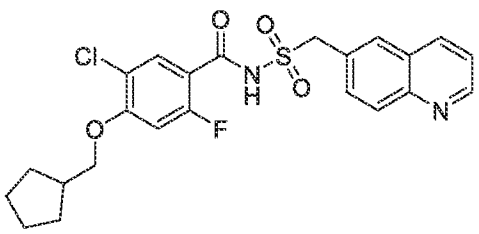


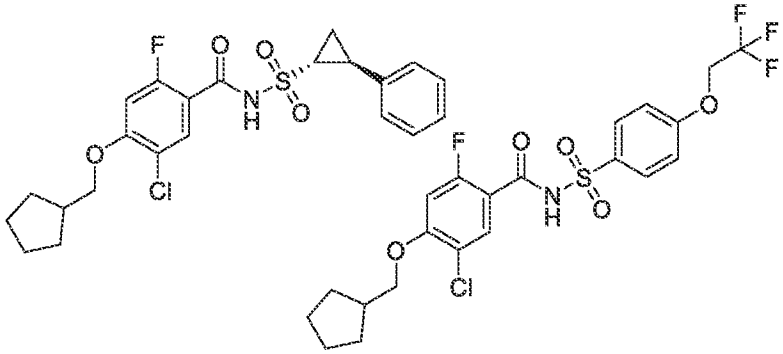


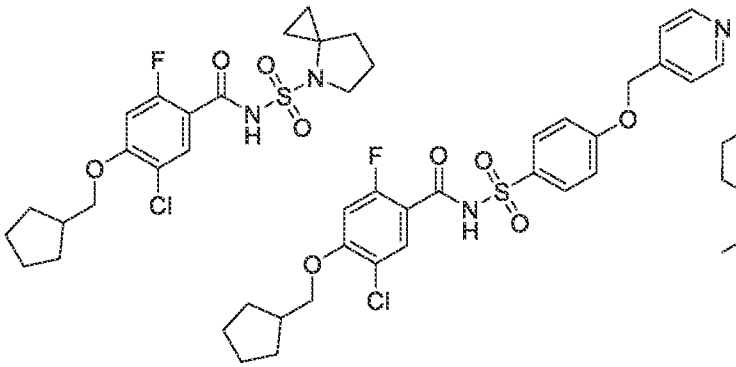


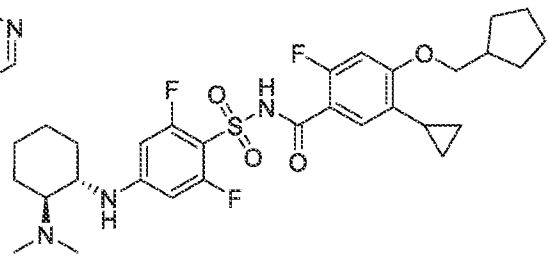


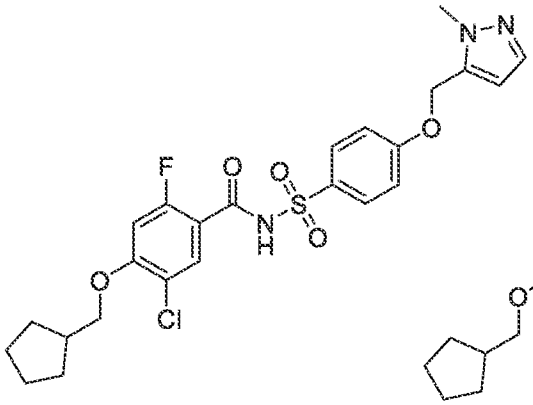


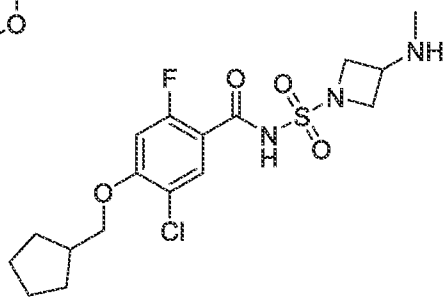


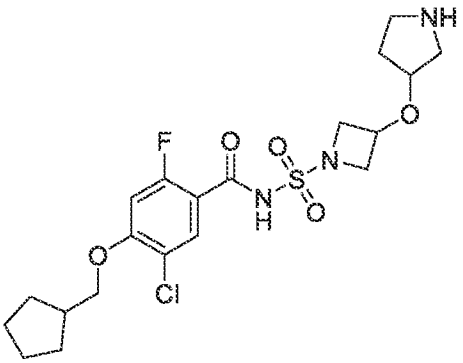


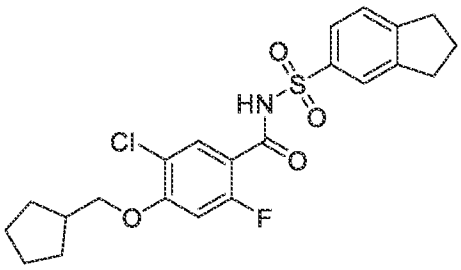


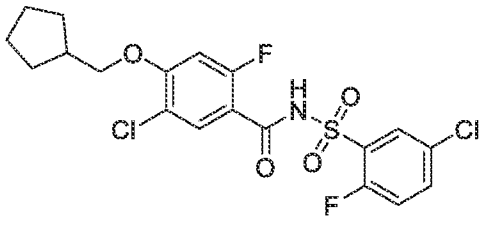


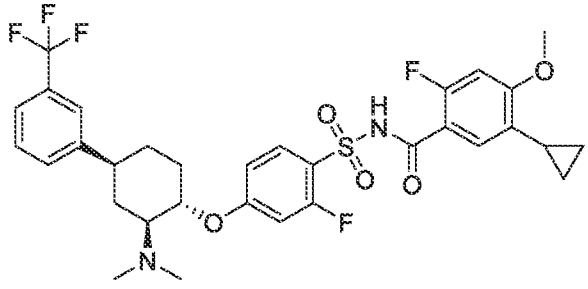


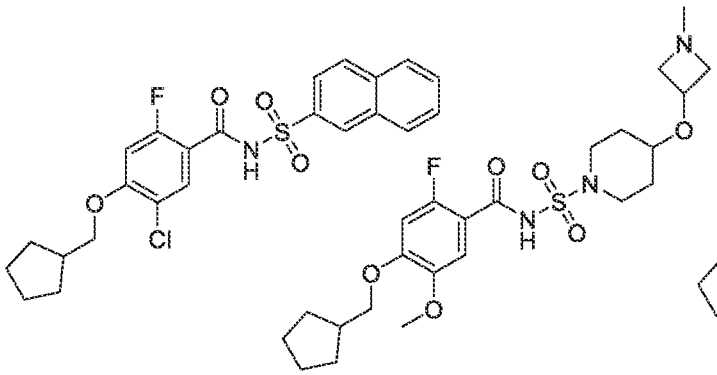


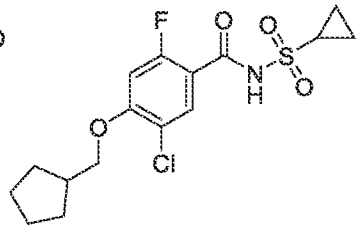


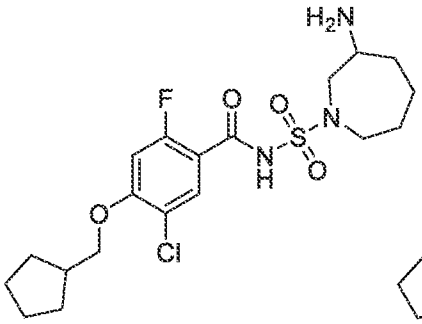


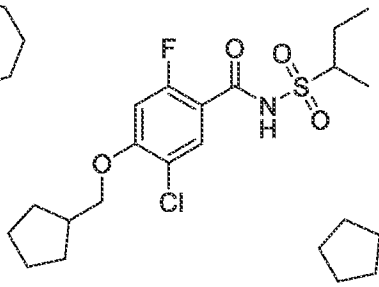


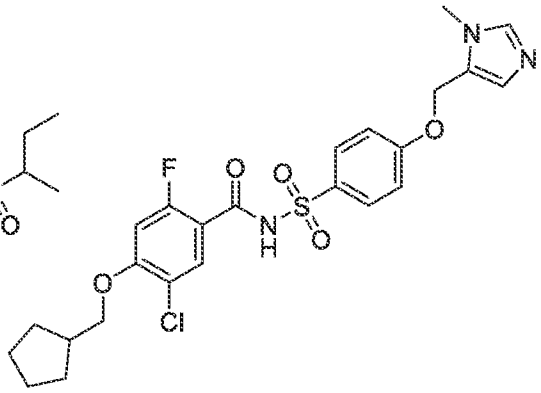


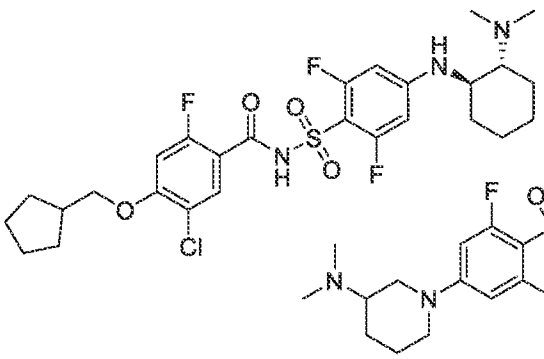


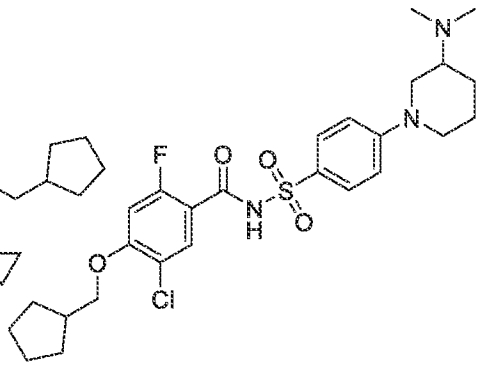


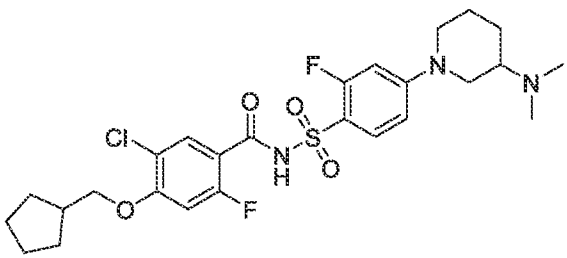


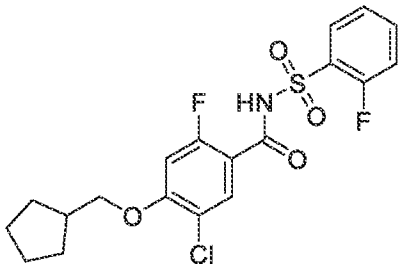


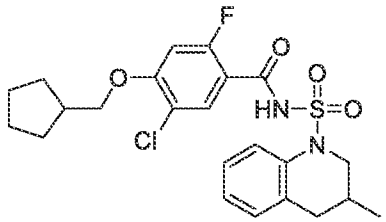


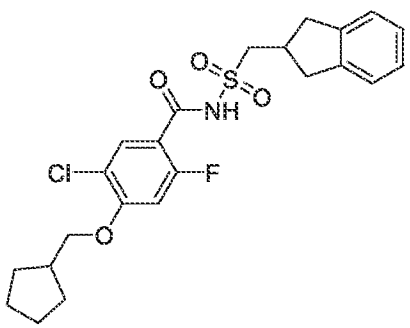


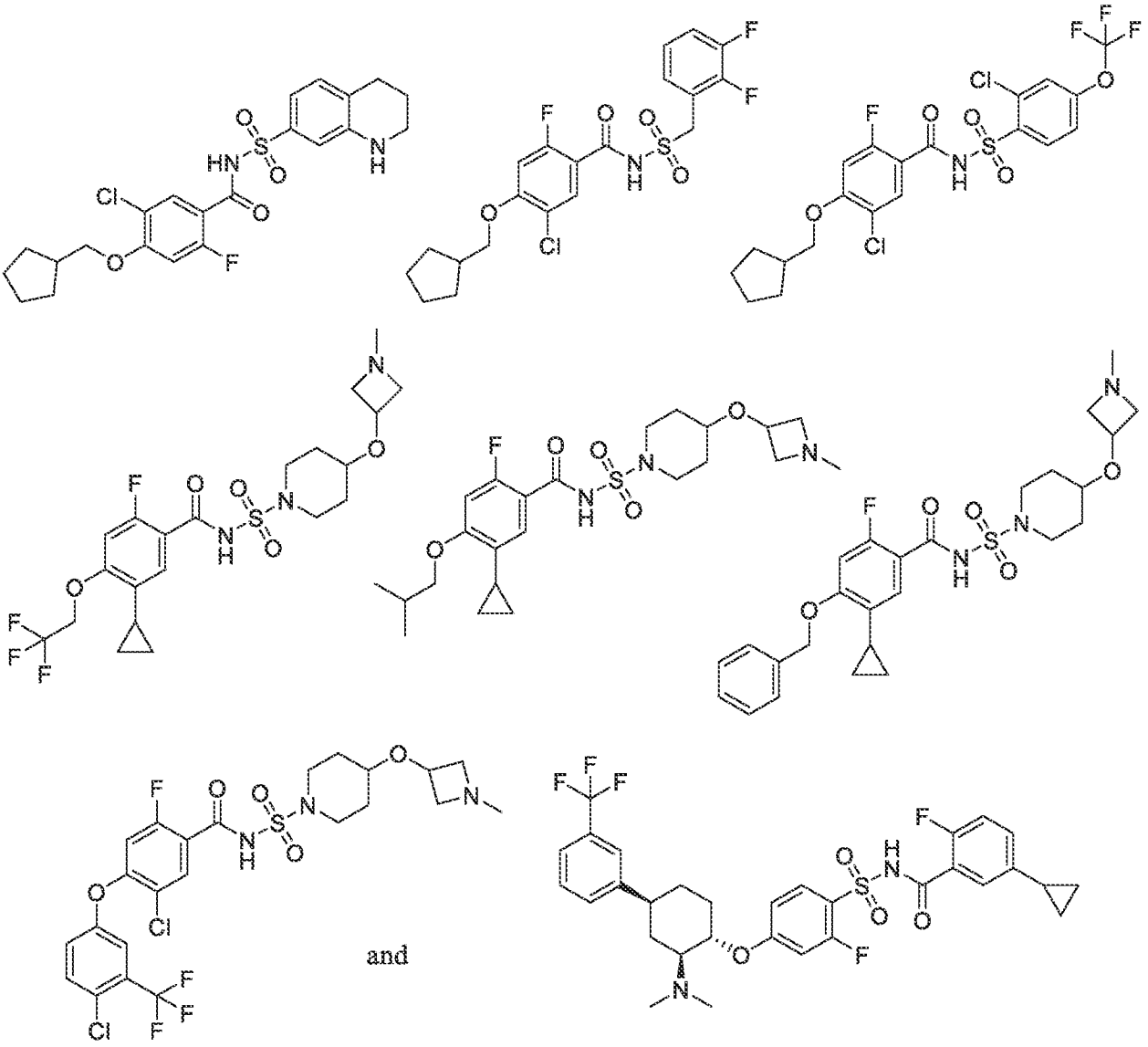








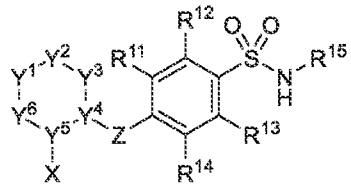




and

and pharmaceutically acceptable salts thereof.

[0039] In another embodiment E22 the invention provides a compound of Formula II or a pharmaceutically acceptable salt thereof, wherein the individual variables are as follows.



(II)

[0040] $\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{13}}$, and $\mathbf{R^{14}}$ are each independently selected from hydrogen, C_1-C_6 alkyl, cyano, C_3-C_6 cycloalkyl, hydroxy, C_1-C_6 alkoxy, $-NH_2$, $-NHR$, $-NR_2$, $-SR$, $-S(O)R$, $-SO_2R$, SO_2NR_2, nitro, and halo,wherein any C_1-C_6 alkyl, and C_3-C_6 cycloalkyl is optionally substituted

with one or more groups independently selected from halo, cyano, hydroxy, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_3-C_6cycloalkyl, and phenyl;

[0041] **Z** is selected from $-N(R^{15})-$, $-O-$, $-S-$, $-S(O)-$, and $-S(O)_2-$;

[0042] $\mathbf{R^{15}}$ is a 9-membered or 10-membered bicyclic heteroaryl that is optionally substituted with from 1 to 5 R^{R15} substituents selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, $-NO_2$, =O, $-X^{15R}NR^{R15a}R^{R15b}$, $-X^{15R}OR^{R15a}$, $-X^{15R}SR^{R15a}$, wherein X^{15R} is C_{1-4} alkylene, or is absent; wherein R^{R15a} and R^{R15b} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-8} alkyl, aryl, (aryl)C_{1-8} alkyl, and C_{2-11} heterocycloalkyl; and where any C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-8} alkyl, aryl, (aryl)C_{1-8} alkyl, and C_{2-11}heterocycloalkyl of R^{R15a} and R^{R15b} is optionally substituted with from 1 to 5 substituents independently selected from the group consisting of C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, and -NO_2;
or $\mathbf{R^{15}}$ is a 5- or 6- membered heterocycle, that is substituted with one or more $-X^{15R}OR^{R15a}$ or $X^{15R}SR^{R15a}$, wherein X^{15R} is C_{1-4} alkylene or is absent; wherein R^{R15a} is hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl,
(C_{3-8}cycloalkyl)C_{1-8} alkyl, phenyl, (aryl)C_{1-8} alkyl, and C_{2-11} heterocycloalkyl; where any C_{2-8} alkenyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-8} alkyl, phenyl, (aryl)C_{1-8} alkyl, and C_{2-11} heterocycloalkyl of R^{R15a} is optionally substituted with from one or more substituents independently selected from the group consisting of C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, and -NO_2;

[0043] **X** is selected from hydrogen, C_{1-8}alkyl, $-N(R^{16})_2$ and $-N(R^{17})_3{}^+W^-$, and amine oxides thereof;

[0044] $\mathbf{W^-}$ is a counterion.

[0045] $\mathbf{Y^1}$ is $-C(R^{18})_2-$; and $\mathbf{Y^2}$ is selected from $-(C(R^{18})_2)_n-$, $-N(R^{19})-$, $-O-$, $-C(R^{18})_2-N(R^{19})-$, $-N(R^{19})-C(R^{18})_2-$, $-C(R^{18})_2-O-$, and $-O-C(R^{18})_2-$; or

[0046] $\mathbf{Y^1}$ is selected from $-N(R^{19})-$ and $-O-$; and $\mathbf{Y^2}$ is $-(C(R^{18})_2)_n-$;

[0047] **n** is selected from 0, 1, and 2;

[0048] $\mathbf{Y^3}$ and $\mathbf{Y^6}$ are each $-C(R^{18})_2-$;

[0049] Y^4 and Y^5 are each $-C(R^{18})-$;

[0050] each R^{16} is independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkanoyl, 4-7 membered heterocycle, 5-6 membered heteroaryl, and C_6-C_{12} aryl, wherein any C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkanoyl, 4-7 membered heterocycle, 5-6 membered heteroaryl, and C_6-C_{12} aryl is optionally substituted with one or more groups independently selected from deuterium, halo, cyano, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_3-C_6 cycloalkyl, C_3-C_6 halocycloalkyl, $-NR^aR^b$, $-C(=O)NR^aR^b$, R^c, and phenyl, wherein any C_1-C_6 alkyl, C_1-C_6 alkoxy, and C_1-C_6 alkanoyl is optionally substituted with C_3-C_6 cycloalkyl; or two R^{16} groups together with the nitrogen to which they are both attached form a 4- to 10-membered heterocycle that is optionally substituted with one or more groups independently selected from deuterium, halo, cyano, hydroxy, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, which C_1-C_6 alkyl, and C_3-C_6 cycloalkyl is optionally substituted with one or more groups independently selected from hydroxy and halo;

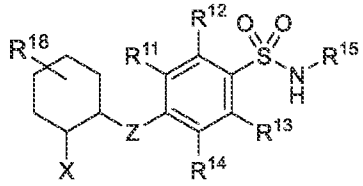
[0051] each R^{17} is independently selected from C_1-C_6 alkyl; or two R^{17} groups together with the nitrogen to which they are both attached form a 4- to 7-membered heterocycle;

[0052] each R^{18} is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, benzyl, 5-15 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_3-C_6 cycloalkoxy, hydroxy, halo, cyano, and $-L$-C_6-C_{12} aryl; wherein each C_3-C_6 cycloalkyl, -L-C_6-C_{12} aryl, benzyl, 5-15 membered heteroaryl, and C_1-C_6 alkoxy, is optionally substituted with one to three substituents R^x each independently selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, cyano, halo, hydroxy, C_3-C_6 cycloalkoxy, C_3-C_6 halocycloalkyl, -S(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -S(O)$_2$(C_1-C_6 alkyl), $-NH_2$, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, 4-6 membered heterocycle, and C_1-C_6 haloalkyl or two R^{18} that are on adjacent carbons taken together form a double bond; and R^{19} is selected from hydrogen, C_1-C_6 alkyl and C_6-C_{12} aryl, which C_6-C_{12} aryl is optionally substituted with one to three substituents each independently selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, cyano, halo, and C_1-C_6 haloalkyl; or one R^{18} or R^{19} taken together with another R^{18} or R^{19} and the atoms to which they are attached form a 3-8 membered fused, bridged or spirocyclic ring, which 3-8 membered ring is optionally substituted with one to three substituents each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, cyano, halo, and C_1-C_6 haloalkyl; and L is selected from a bond, $-O-$, $-S-$, $-S(O)-$, and $-S(O)_2-$;

[0053] each R^a and R^b is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_1-C_6 alkanoyl;

[0054] each R^c is independently selected from 4-7 membered heterocycle that is optionally substituted with one or more groups independently selected from halo, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; and

[0055] In another embodiment E23, the invention provides a compound or pharmaceutically acceptable salt of embodiment E22, which is a compound of formula IIa, wherein X, Z, R^{11} – R^{15} and R^{18} are as for formula II:



IIa

or a pharmaceutically acceptable salt thereof.

[0056] In another embodiment E24, the invention provides a compound or pharmaceutically acceptable salt of E22 or E23, wherein R^{18} is trifluoromethyl or phenyl that is optionally substituted with one to three substituents each independently selected from C_1-C_6 alkyl, cyano, halo, and C_1-C_6 haloalkyl; or a pharmaceutically acceptable salt thereof.

[0057] In another embodiment E25, the invention provides a compound or pharmaceutically acceptable salt of E22, E23 or E24, wherein X is $-N(R^{16})_2$ and each R^{16} is independently selected from hydrogen, C_2-C_6 alkoxyalkyl, C_1-C_6 alkyl, benzyl, C_3-C_6cycloalkyl, C_1-C_6haloalkyl, and C_1-C_6hydroxyalkyl; or a pharmaceutically acceptable salt thereof.

[0058] In another embodiment E26, the invention provides a compound or pharmaceutically acceptable salt of E22, E23 or E24 wherein X is $-N(R^{16})_2$ and two R^{16} groups together with the nitrogen to which they are both attached form a 4- to 7-membered heterocycle, or a pharmaceutically acceptable salt thereof.

[0059] In another embodiment E27, the invention provides a compound or pharmaceutically acceptable salt of E22, E23, or E24, wherein X is dimethylamino, or a pharmaceutically acceptable salt thereof.

[0060] In another embodiment E28, the invention provides a compound or pharmaceutically acceptable salt of E22, E23, E24, E25, E26, or E27, wherein any of R^{11}, R^{12}, R^{13}, or R^{14} is selected from fluoro, chloro, bromo, cyclopropyl, and trifluoromethyl; or a pharmaceutically acceptable salt thereof.

[0061] In another embodiment E29, the invention provides a compound or pharmaceutically acceptable salt of E22, E23, E24, E25, E26, E27, or E28, wherein R^{11} is H, or a pharmaceutically acceptable salt thereof.

[0062] In another embodiment E30, the invention provides a compound or pharmaceutically acceptable salt of E22, E23, E24, E25, E26, E27, or E28, wherein R^{11} is selected from hydrogen and halo; or a pharmaceutically acceptable salt thereof.

[0063] In another embodiment E31, the invention provides a compound or pharmaceutically acceptable salt of E22, E23, E24, E25, E26, E27, E28, E29 or E30, wherein R^{13} is selected from hydrogen and fluoro; or a pharmaceutically acceptable salt thereof.

[0064] In another embodiment E32, the invention provides a compound or pharmaceutically acceptable salt of E22, E23, E24, E25, E26, E27, E28, E29, E30, or E31 wherein R^{12} is hydrogen; or a pharmaceutically acceptable salt thereof.

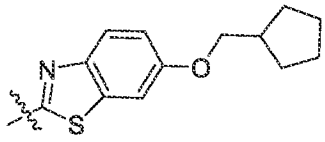
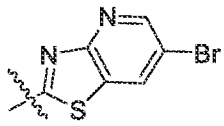
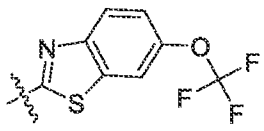
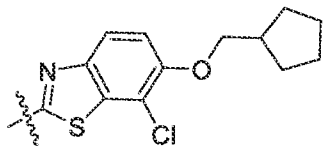
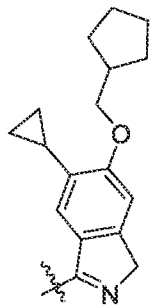
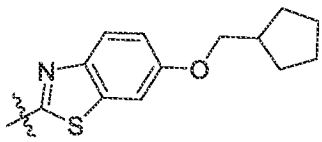
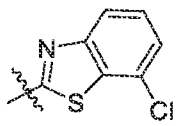
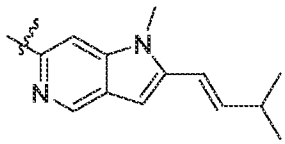
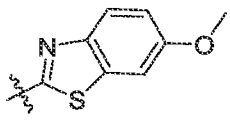
[0065] In another embodiment E33, the invention provides a compound or pharmaceutically acceptable salt of E22, E23, E24, E25, E26, E27, E28, E29, E30, E31, or E32, wherein R^{14} is hydrogen; or a pharmaceutically acceptable salt thereof.

[0066] In another embodiment E34, the invention provides a compound or pharmaceutically acceptable salt of E22, E23, E24, E25, E26, E27, E29, E30, E31, or E32, wherein R^{11}, R^{12}, R^{13}, or R^{14} is selected from hydrogen, fluoro, chloro, bromo, cyclopropyl, cyclobutyl, hydroxy, methoxy, and trifluoromethyl; or a pharmaceutically acceptable salt thereof.

[0067] In another embodiment E35, the invention provides a compound or pharmaceutically acceptable salt of E22, E23, E24, E25, E26, E27, E28, E29, E30, E31, E32, E33, or E34, wherein R^{15} is a 9-membered or 10-membered bicyclic heteroaryl that is optionally substituted with from 1 to 5 R^{R15} substituents selected from the group consisting of C_{1-8} alkyl, C_{2-8} alkenyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, -NO_2, =O, -$(X^{15R})_{0-1}NR^{R15a}R^{R15b}$, -$(X^{15R})_{0-1}OR^{R15a}$, -$(X^{15R})_{0-1}SR^{R15a}$, wherein X^{15R} is C_{1-4} alkylene; wherein R^{R15a} and R^{R15b} are independently selected from the group consisting of hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, (C_{3-8}

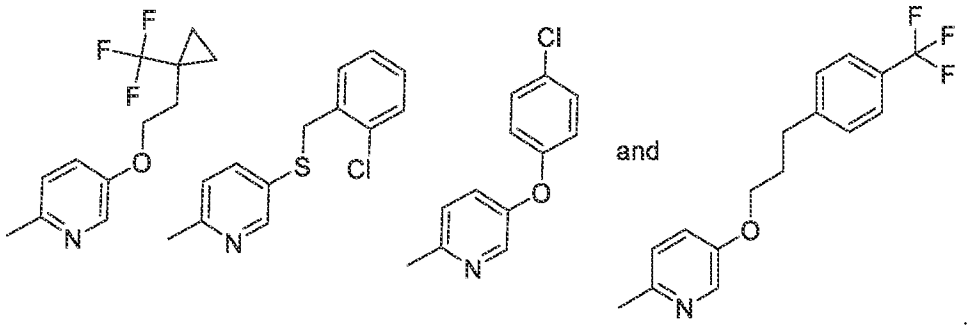
cycloalkyl)C_{1-8} alkyl, aryl, (aryl)C_{1-8} alkyl, and C_{2-11} heterocycloalkyl; and where any C_{2-8} alkenyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-8} alkyl, phenyl, (aryl)C_{1-8} alkyl, and C_{2-11} heterocycloalkyl of R^{R15a} and R^{R15b} is optionally substituted with from 1 to 5 substituents independently selected from the group consisting of C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, and -NO_2.

[0068] In another embodiment E36, the invention provides a compound or pharmaceutically acceptable salt of E22, E23, E24, E25, E26, E27, E28, E29, E30, E31, E32, E33. E34, or E35, wherein R^{15} is selected from the group consisting of:









and 

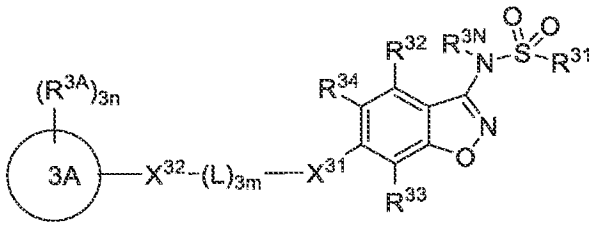
[0069] In another embodiment E37, the invention provides a compound or pharmaceutically acceptable salt of E22, E23, E24, E25, E26, E27, E28, E29, E30, E31, E32, E33. E34, or E35, wherein R^{15} is a heterocycle selected from thiazole, thiadiazole, oxazole, isoxazole, pyrimidine, pyridazine, and pyridyl, wherein the heterocycle is substituted with one or more -$(X^{15R})_{0-1}OR^{R15a}$ or -$(X^{15R})_{0-1}SR^{R15a}$, wherein X^{15R} is C_{1-4} alkylene; wherein R^{R15a} is hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-8} alkyl, phenyl, (aryl)C_{1-8} alkyl, and C_{2-11} heterocycloalkyl; where any C_{2-8} alkenyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl)C_{1-8} alkyl, phenyl, (aryl)C_{1-8} alkyl, and C_{2-11} heterocycloalkyl of R^{R15a} is optionally substituted with from 1 to 5 substituents independently selected from the group consisting of C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, and -NO_2.

[0070] In another embodiment E38, the invention provides a compound or pharmaceutically acceptable salt of E22, E23, E24, E25, E26, E27, E28, E29, E30, E31, E32, E33, or E34, wherein R^{15} is selected from the group consisting of:



[0071] In another embodiment E40, the invention provides a compound or pharmaceutically acceptable salt of E22 selected from the group consisting of the compounds described in the individual Examples herein, including but not limited to the compounds of Examples 89, 95, 96, 97, 99, 101, 102, 103, 201 202, 203, 257, 258, and 333, and pharmaceutically acceptable salts thereof, wherein it is intended that, where specific chirality is not designated at a given chiral center, then either enantiomer or diastereomer of the depicted compound is encompassed.

[0072] In another embodiment E41 the invention provides a compound of the invention, which is a compound of Formula III:



III

or a pharmaceutically acceptable salt thereof, wherein the individual variables are as follows.

[0073] R^{31} is selected from a first set of moieties consisting of C_{1-8}alkyl, C_{3-12}cycloalkyl, C-linked C_{2-11}heterocycloalkyl, C_{3-12}carbocycle, aryl, heteroaryl, and $-NR^{31A}R^{31B}$, wherein:

R^{31A} and R^{31B} are selected from H, C_{1-8}alkyl, C_{3-8}cycloalkyl, C_{1-8}haloalkyl, or R^{31A} and R^{31B} together with the nitrogen atom to which they are both bonded form a 3 to 10 membered heterocyclic group;

any of the first set of moieties, R^{31A}, or R^{31B}, is optionally substituted with one or more substituents selected from a second set of moieties consisting of:

C_{1-8}alkyl, C_{2-8}alkenyl, C_{3-8}cycloalkyl, C_{1-8}haloalkyl, aryl, (aryl)C_{1-8}alkyl, heteroaryl, (heteroaryl)C_{1-8}alkyl, C_{2-11}heterocycloalkyl, (C_{2-11}heterocycloalkyl)C_{1-8}alkyl, F, Cl, Br, I, –OH, –CN, $–NO_2$, =O, aminocarbonyl, $–X^{R1}NR^{R1a}R^{R1b}$, $–X^{R1}OR^{R1a}$, and $–X^{R1}SR^{R1a}$, wherein:

X^{R1} is selected from the group consisting of C(=O), C_{1-4} alkylene, C_{1-4}heteroalkylene, C_{2-4}alkenylene and C_{2-4} alkynylene, or is absent; and R^{R1a} and R^{R1b} are independently selected from a third set of moieties consisting of: H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{1-8}haloalkyl, C_{3-8}cycloalkyl, C_{3-12}carbocycle, (C_{3-8} cycloalkyl)C_{1-8} alkyl, aryl, (aryl)C_{1-8}alkyl, heteroaryl, (heteroaryl)C_{1-8}alkyl, C_{2-11}heterocycloalkyl, and (C_{2-11}heterocycloalkyl)C_{1-8}alkyl,
or R^{R1a} and R^{R1b} together with the nitrogen atom to which they are both bonded form a 3 to 10 membered heterocyclic group;

and

wherein any of the second set of moieties, R^{R1a}, or R^{R1b}, where present, are each optionally substituted by one or more groups independently selected from: C_{1-8} alkyl, C_{1-8}haloalkyl, F, Cl, Br, I, -OH, -CN, aryl, C_{1-8}haloalkyl-substituted aryl, C_{1-8}alkoxy, C_{1-8}alkanoyl, C_{1-8}alkoxycarbonyl, C_{3-8}cycloalkyl, C_{2-11}heterocycloalkyl, amino, (C_{1-3}alkyl)amino, di(C_{1-3}alkyl)amino, C_{1-3}alkylamido, C_{1-3}alkylcarboxy, and -NO_2;

[0074] $\mathbf{R^{3N}}$ is hydrogen, C_{1-4} alkyl or C_{1-4} haloalkyl.

[0075] $\mathbf{R^{32}}$ and $\mathbf{R^{33}}$ are independently selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl and C_{1-8} alkoxy.

[0076] $\mathbf{R^{34}}$ is selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{2-11} heterocycloalkyl, phenyl and 5-6 membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O and S, wherein said 5-6 membered heteroaryl, C_{1-8} alkyl, C_{3-8} cycloalkyl or C_{2-11} heterocycloalkyl is further optionally substituted with from 1 to 3 R^{5a} substituents selected from F, Cl, Br, I, -OH , =O, C_{3-6} cycloalkyl, -CN, C_{1-4} alkyl, -C_{1-4} alkyl-O-C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} alkoxy.

[0077] **L** is a linker selected from the group consisting of C_{1-4} alkylene, C_{2-4} alkenylene, C_{2-4} alkynylene, and C_{1-4} heteroalkylene, wherein L is optionally substituted with from 1 to 3 substituents selected from the group consisting of =O, -OH, -OCH_2-phenyl, C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} acyl.

[0078] **3m** is 0 or 1.

[0079] **3n** is an integer from 0 to 5.

[0080] X^{31} and X^{32} are each independently selected from the group consisting of –O–, –S(O)–, –S(O)$_2$– and –N(R^X)– wherein R^X is H, C_{1-8} alkyl, C_{1-8} acyl or -S(O)$_2$(C_{1-8} alkyl), or is absent, and wherein if 3m is 0 then at least one of X^{31} or X^{32} is absent.

[0081] **3A** is selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8}haloalkyl, C_{3-12} cycloalkyl, and aryl, and wherein if 3A is hydrogen then n is 0.

[0082] each R^{3A} is independently selected from the group consisting of C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, -NO_2, and =O.

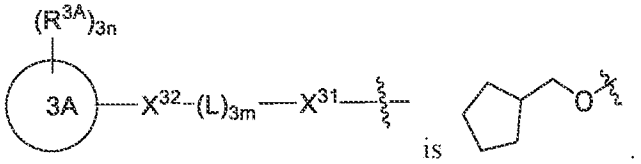
[0083] In another embodiment E42, the invention provides a compound or pharmaceutically acceptable salt of E41, wherein X^{31} is -O-.

[0084] In another embodiment E43, the invention provides a compound or pharmaceutically acceptable salt of E41 or E42, wherein X^{32} is absent.

[0085] In another embodiment E44, the invention provides a compound or pharmaceutically acceptable salt of E41, E42, or E43, wherein **L** is C_{1-4} alkylene.

[0086] In another embodiment E45, the invention provides a compound or pharmaceutically acceptable salt of E41, E42, or E43, wherein **L** is methylene.

[0087] In another embodiment E46, the invention provides a compound or pharmaceutically acceptable salt of E41, wherein the group



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[0088] In another embodiment E47, the invention provides a compound or pharmaceutically acceptable salt of E41, E42, E43, E44, E45, or E46, wherein R^{32} is H.

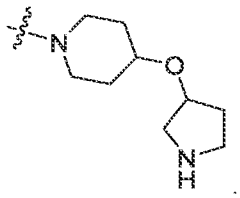
[0089] In another embodiment E48, the invention provides a compound or pharmaceutically acceptable salt of E41, E42, E43, E44, E45, E46, or E47, wherein R^{33} is H.

[0090] In another embodiment E49, the invention provides a compound or pharmaceutically acceptable salt of E41, E42, E43, E44, E45, E46, E47, or E48, wherein R^{34} is selected from the group consisting of F, Cl, ethyl, isopropyl, cyclopropyl, and methoxy.

[0091] In another embodiment E50, the invention provides a compound or pharmaceutically acceptable salt of E41, E42, E43, E44, E45, E46, E47, or E48, wherein $\mathbf{R^{34}}$ is selected from the group consisting of Cl and cyclopropyl.

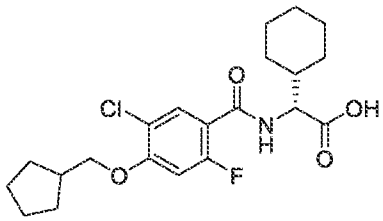
[0092] In another embodiment E51, the invention provides a compound or pharmaceutically acceptable salt of E41, E42, E43, E44, E45, E46, E47, E48, E49, or E50, wherein $\mathbf{R^{N}}$ is hydrogen.

[0093] In another embodiment E52, the invention provides a compound or pharmaceutically acceptable salt of E41, E42, E43, E44, E45, E46, E47, E48, E49, E50, or E51, wherein $\mathbf{R^{31}}$ is:



[0094] In another embodiment E53, the invention provides a compound or pharmaceutically acceptable salt of E41 that is that is selected from the group consisting of compounds described in the individual Examples herein, including but not limited to the compounds of Examples 89, 90, 91, 93 and 94, and pharmaceutically acceptable salts thereof, wherein it is intended that, where specific chirality is not designated at a given chiral center, then either enantiomer or diastereomer of the depicted compound is encompassed.

[0095] In another embodiment E54 the invention provides a compound having the following structure:



or a pharmaceutically acceptable salt thereof.

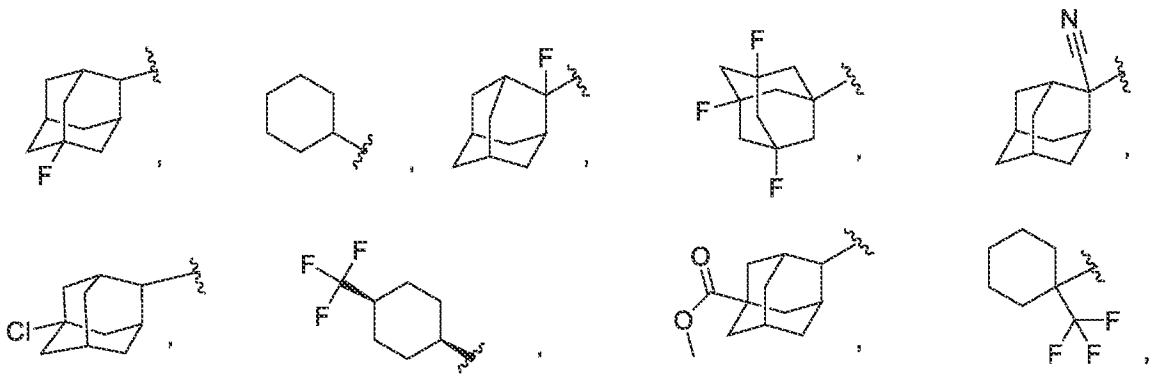
[0096] In another embodiment E55, the invention provides a compound or pharmaceutically acceptable salt of embodiments E1 – E20 of Formula (I), wherein X^1 is –O- or –N(H)-; X^2 is absent; m is 1; and L is selected from the group consisting of –CH_2-, –C(=O)-, –C(H)(CH_3)-, –CH_2-CH_2-, –CH_2-C(H)(CH_3)-, –C(H)(CH_3)-C(H_2)-, –$CH_2CH_2CH_2$-, –CH_2-C(H)(CH_3)-CH_2- or -$CH_2CH_2CH_2CH_2$-.

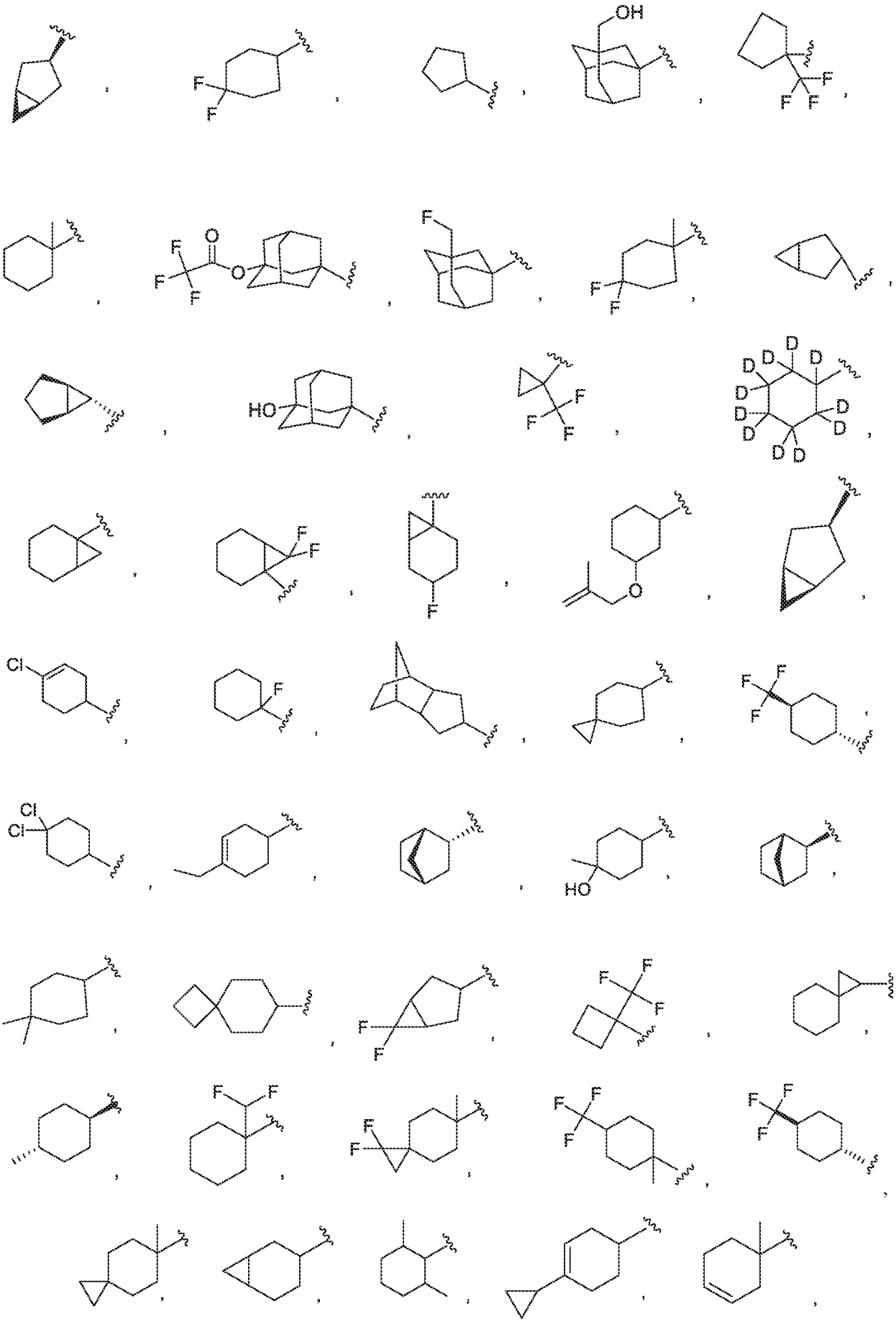
[0097] In another embodiment E56, the invention provides a compound or pharmaceutically acceptable salt of embodiments E1 – E20 of Formula (I), wherein A is an optionally substituted ring selected from the group consisting of cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, adamantane, bicyclo[2.1.1]hexane, bicyclo[2.2.2]octane, bicyclo[2.2.1]heptane, bicyclo[3.1.1]heptane, bicyclo[3.2.1]octane, bicyclo[4.1.1]octane, bicyclo[3.3.1]nonane and 1,2,3,4-tetrahydro-1,4-methanonaphthalene, 1,2,3,4-tetrahydroisoquinoline and chroman.

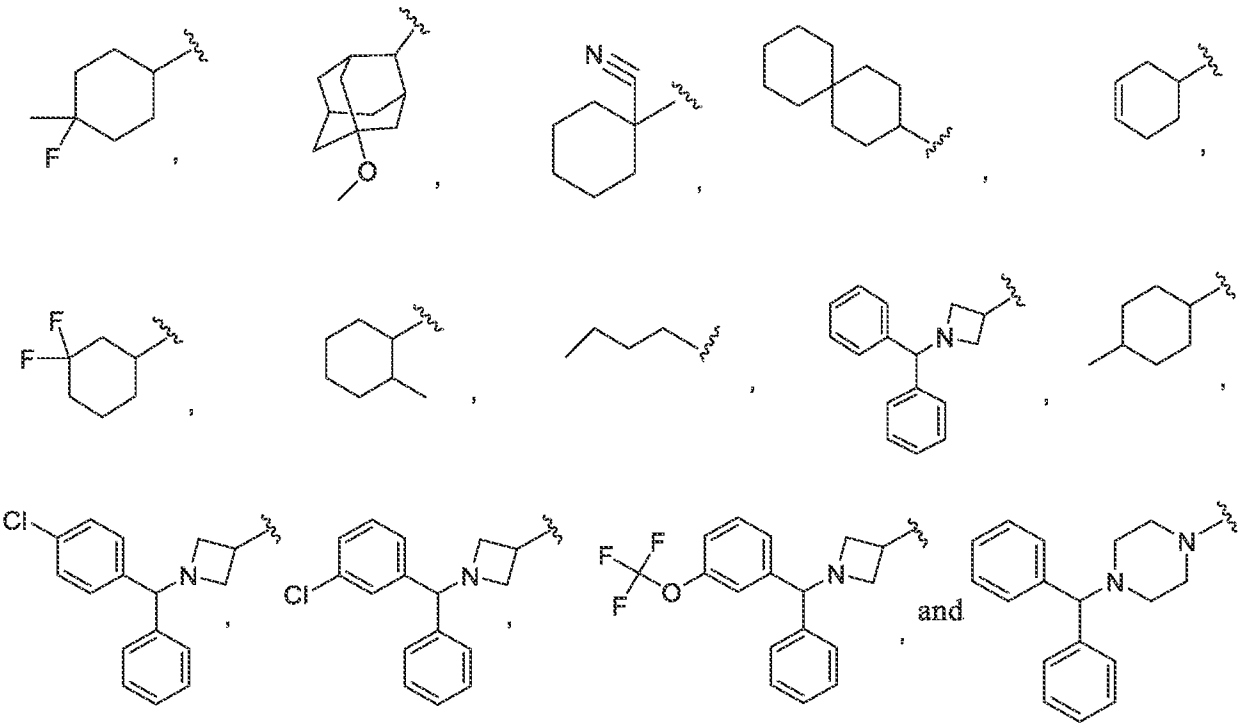
[0098] In another embodiment E57, the invention provides a compound or pharmaceutically acceptable salt of embodiments E1 – E20 of Formula (I), wherein A is an optionally substituted ring selected from the group consisting of cyclopropane, cyclobutane, cyclopentane, cyclohexane, adamantane, cubane, bicyclo[2.2.2]octane, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, piperidinyl, tetrahydrofuranyl, tetrahydronaphthyl, spiro[2,5]octanyl, norpinanyl, spiro[3.5]nonanyl, 8-azabicyclo[3.2.1]octanyl, norbornanyl, spiro[4.5]decanyl, bicyclo[4.1.0]heptane and spiro[5.5]undecanyl.

[0099] In another embodiment E58, the invention provides a compound or pharmaceutically acceptable salt of embodiments E1 – E20 of Formula (I), wherein A is an optionally substituted ring selected from the group consisting of azetidine, pyrrolidine, piperidine, homopiperidine, (1R,5S)-8-azabicyclo[3.2.1]octane, 3-oxa-9-azabicyclo[3.3.1]nonane, (1s,4s)-7-azabicyclo[2.2.1]heptane, (1R,4S)-5-azabicyclo[2.1.1]hexane, 7-(trifluoromethyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine and quinuclidine.

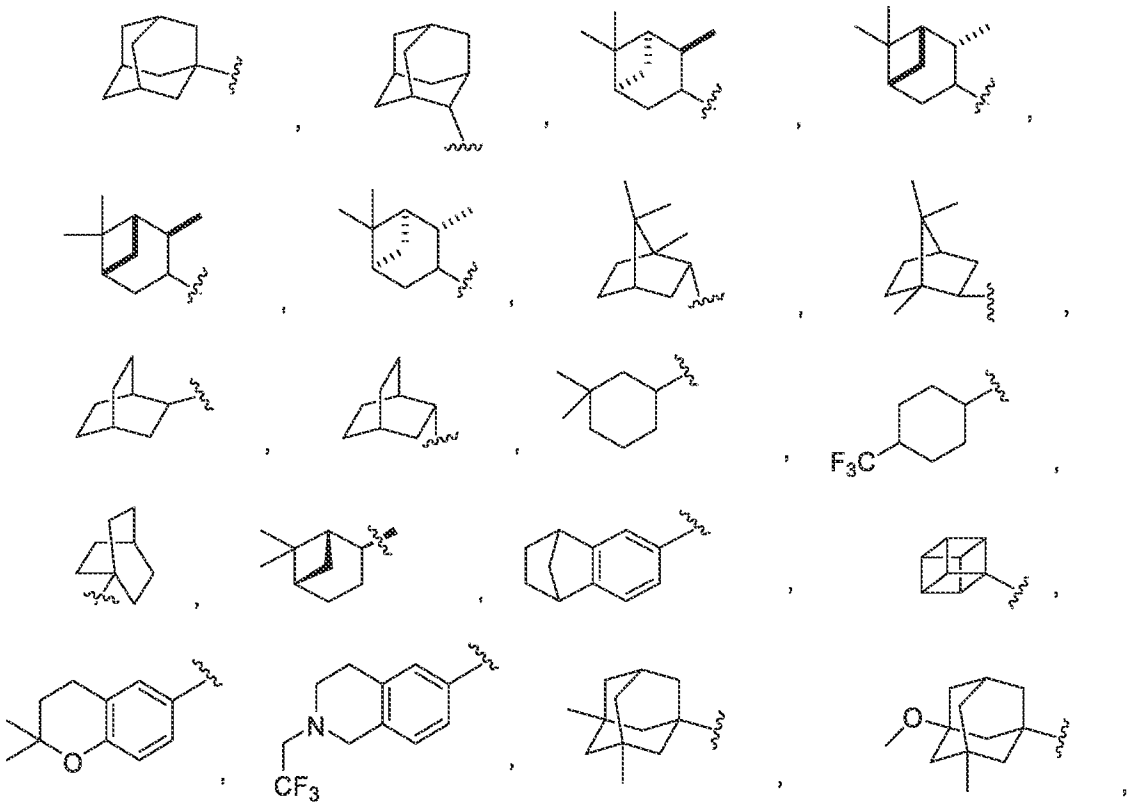
[0100] In another embodiment E59, the invention provides a compound or pharmaceutically acceptable salt of embodiments E1 – E20 of Formula (I), wherein A-$(R^A)_n$ is selected from the group consisting of:

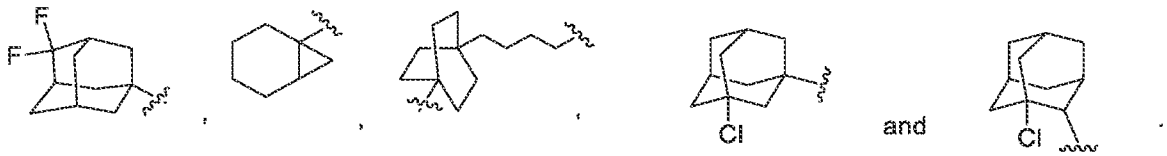




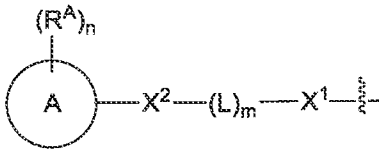


[0101] In another embodiment E60, the invention provides a compound or pharmaceutically acceptable salt of embodiments E1 – E20 of Formula (I), wherein A-$(R^A)_n$ is selected from the group consisting of:

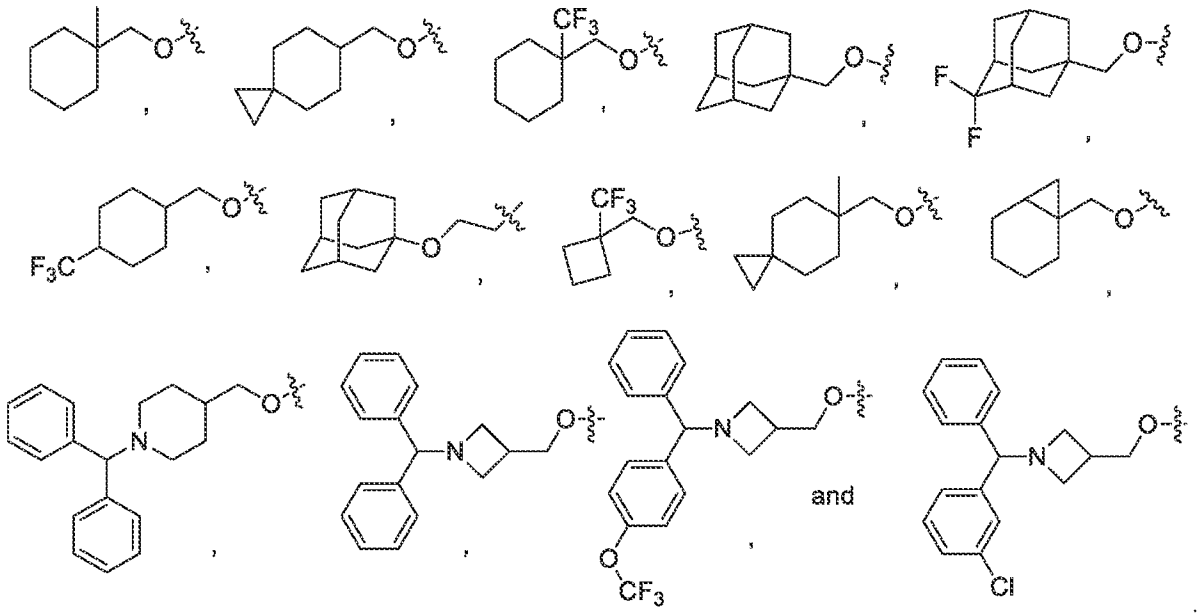




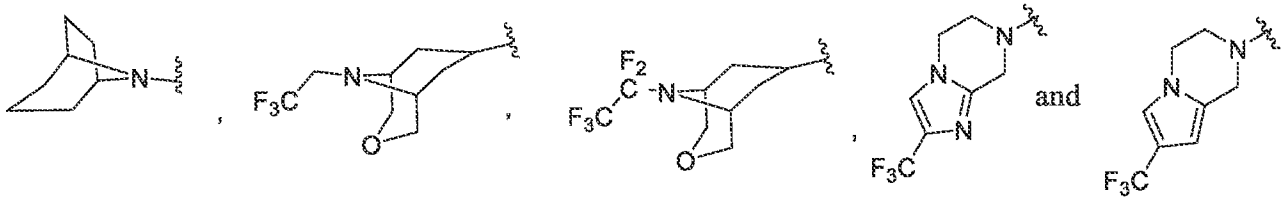
[0102] In another embodiment E61, the invention provides a compound or pharmaceutically acceptable salt of embodiments E1 – E20 of Formula (I), wherein the group



is selected from the group consisting of:



[0103] In another embodiment E62, the invention provides a compound or pharmaceutically acceptable salt of embodiments E1 – E20 of Formula (I), wherein $A(R^A)_n$ is selected from the group consisting of:



[0104] In another aspect the present invention provides for a pharmaceutical composition comprising a compound of formulae (I), (II), and (III), as described herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0105] In another aspect the present invention provides for a method of treating a disease or condition in a mammal selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, and combinations thereof, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt thereof. In another aspect of the present invention said disease or condition is selected from the group consisting of neuropathic pain, inflammatory pain, visceral pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, neurogenic bladder, ulcerative colitis, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, dental pain, peripheral nerve injury or a combination thereof. In another aspect of the present invention said disease or condition is selected from the group consisting of pain associated with HIV, HIV treatment induced neuropathy, trigeminal neuralgia, post-herpetic neuralgia, eudynia, heat sensitivity, tosarcoidosis, irritable bowel syndrome, Crohns disease, pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), diabetic neuropathy, peripheral neuropathy, arthritis, rheumatoid arthritis, osteoarthritis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxin related illnesses, familial erythromelalgia, primary erythromelalgia, familial rectal pain, cancer, epilepsy, partial and general tonic seizures, restless leg syndrome, arrhythmias, fibromyalgia, neuroprotection under ischaemic conditions cause by stroke or neural trauma, tach-arrhythmias, atrial fibrillation and ventricular fibrillation.

[0106] In another aspect the present invention provides for a method of treating pain in a mammal by the inhibition of ion flux through a voltage-dependent sodium channel in the mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt thereof.

[0107] In another aspect the present invention provides for a method of decreasing ion flux through a voltage-dependent sodium channel in a cell in a mammal, wherein the method comprises contacting the cell with a compound as described herein, or a pharmaceutically acceptable salt thereof.

[0108] In another aspect the present invention provides for a method of treating pruritus in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

[0109] In another aspect the present invention provides for a method of treating cancer in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount a compound as described herein, or a pharmaceutically acceptable salt thereof.

[0110] In another aspect the present invention provides for a method of treating, but not preventing, pain in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt thereof. In another aspect of the present invention the pain is selected from the group consisting of neuropathic pain, inflammatory pain, visceral pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, neurogenic bladder, ulcerative colitis, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, dental pain, peripheral nerve injury or a combination thereof. In another aspect the present invention the pain is associated with a disease or condition selected from the group consisting of HIV, HIV treatment induced neuropathy, trigeminal neuralgia, post-herpetic neuralgia, eudynia, heat sensitivity, tosarcoidosis, irritable bowel syndrome, Crohns disease, pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), diabetic neuropathy, peripheral neuropathy, arthritis, rheumatoid arthritis, osteoarthritis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxin related illnesses, familial erythromelalgia, primary erythromelalgia, familial rectal pain, cancer, epilepsy, partial and general tonic seizures, restless leg syndrome, arrhythmias, fibromyalgia, neuroprotection under ischaemic conditions cause by stroke or neural trauma, tach-arrhythmias, atrial fibrillation and ventricular fibrillation.

[0111] In another aspect the present invention provides for a method for the treatment or prophylaxis of pain, depression, cardiovascular disease, respiratory disease, or psychiatric disease, or a combinations thereof, in an animal which method comprises administering an effective amount of a compound of as described herein, or a pharmaceutically acceptable salt thereof.

[0112] In another aspect the present invention provides for a compound as described herein, or a pharmaceutically acceptable salt thereof for the use as a medicament for the treatment of diseases and disorders selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, or a combination thereof.

[0113] In another aspect the present invention provides for the use of a compound as described herein, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of diseases and disorders selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, or a combination thereof.

[0114] In another aspect the present invention includes methods of designing NaV1.7 inhibitors utilizing computational methods that utilize virtual "docking" of test molecules into a computer model of the binding site.

[0115] A still further aspect of the invention is a method of identifying a compound that binds to the NaV1.7 receptor, wherein the method comprises: modeling test compounds that fit spatially into a NaV1.7 binding site using an atomic structural model of the NaV1.7 receptor binding site or portion thereof, screening the test compounds in an assay, for example a biological assay, characterized by measuring binding of a test compound to the NaV1.7 receptor, and identifying a test compound that binds according to a threshold, such as at least 1 micromolar, at least 0.1 micromolar, at least 0.001 micromolar. The atomic structural model comprises atomic coordinates of a NaV1.7 receptor and may additionally comprise coordinates of a ligand bound to the NaV1.7 binding site. It is to be understood that the atomic structural model may comprise the entire Nav1.7 receptor, or simply a sufficient portion thereof that comprises coordinates of the binding site.

BRIEF DESCRIPTION OF THE FIGURES

[0116] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0117] FIG. 1 shows attempts to rationalize the binding behavior of two classes of NaV1.7 binding compounds from the prior art.

[0118] FIGs. 2A and 2B show schematics of binding poses of aryl- and acyl-sulfonamide compounds of the prior art.

[0119] FIG. 3A shows a schematic of design of compounds of the present invention, and FIG. 3B shows highlighted portions of the NaV1.7 VSD4 binding pocket and binding poses for 3 classes of compound.

[0120] FIG. 4 shows exemplary structural components of compounds of the present invention.

[0121] FIGs. 5A, 5B and 5C show a schematic of the binding configuration of the compound of Example 59 from an extracellular view, and an arginine core view, and showing the reduced extent of interaction between ligand and Try1537.

[0122] FIGs. 6A ("Cyclopropane substitution expectedly improves potency"), 6B ("Lipophilic piece can be transposed from one location to another") and 6C ("compounds are inactive without lipophilic piece") show schematics of aspects of SAR based on hybrid structured molecules.

[0123] FIG. 7A, 7B, 7C, 7D, and 7E show instances of aryl-sulfonamide binding that exhibit preferential interactions to acyl-sulfonamide compounds.

[0124] FIGs. 8A and 8B, illustrate aspects of designing molecules to compensate for the energetic penalty associated with helix rearrangement upon binding, within the VSD4 binding domain.

[0125] FIG. 9 panels A and B show cryoEM data from Example 403 for the compound of Example 96: A: Sample freezing; B: 2D classification.

[0126] FIG. 10 shows data from cryo-EM analyses in Example 403.

DETAILED DESCRIPTION

Definitions

[0127] As used herein, the term "alkyl", by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain hydrocarbon radical, having the number of carbon atoms designated (i.e., $C_{1\text{-}8}$ means one to eight carbons). Examples of alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl, iso-butyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like.

[0128] The term "alkoxy" is used in its conventional sense, and refers to an alkyl group attached to the remainder of the molecule via an oxygen atom ("oxy").

[0129] The term "alkylthio" is used in its conventional sense, and refers to an alkyl group attached to the remainder of the molecule via a sulfur atom.

[0130] The terms "halo" by itself or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom.

[0131] The term "haloalkyl" refers to an alkyl that is substituted with one or more (e.g. 1, 2, 3, 4, 5, or 6) halo groups. For example the term includes an alkyl group having 1-6 carbon atoms that is substituted with one or more halo groups. Non-limiting examples of the term C_1-C_6 haloalkyl include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, and 2,2,2-trifluoroethyl.

[0132] The term "(haloalkyl)thio" refers to an alkyl that is substituted with one or more (e.g. 1, 2, 3, 4, 5, or 6) halo groups and is attached to the remainder of the molecule via a sulfur atom.

[0133] The term "halocycloalkyl" refers to a cycloalkyl that is substituted with one or more (e.g. 1, 2, 3, 4, 5, or 6) halo groups. For example the term includes a cycloalkyl group having 3-6 carbon atoms that is substituted with one or more halo groups. Non-limiting examples of the term C_1-C_6 halocycloalkyl include 1-fluorocyclopropyl.

[0134] The term "aryl" as used herein refers to a single all carbon aromatic ring or a multiple condensed all carbon ring system wherein at least one of the rings is aromatic. For example, in certain embodiments, an aryl group has 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 12 carbon atoms. Aryl includes a phenyl radical. Aryl also includes multiple condensed ring systems (e.g., ring systems comprising 2, 3 or 4 rings) having about 9 to 20 carbon atoms in which at least one ring is aromatic and wherein the other rings may be aromatic or not aromatic (i.e., carbocycle). Such multiple condensed ring systems are optionally substituted with one or more (e.g., 1, 2 or 3) oxo groups on any carbocycle portion of the multiple condensed ring system. The rings of the multiple condensed ring system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. It is to be understood that the point of attachment of a multiple condensed ring system, as defined above, can be at any position of the ring system including an aromatic or a carbocycle portion of the ring. Non-limiting examples of aryl groups include, but are not limited to, phenyl, indenyl, naphthyl, 1, 2, 3, 4-tetrahydronaphthyl, anthracenyl, and the like.

[0135] The term "(aryl)alkyl" as used herein refers to an aryl group that is attached through an alkyl group (e.g., benzyl or phenethyl).

[0136] The term "carbocycle" or "carbocyclyl" refers to a single saturated (i.e., cycloalkyl) or a single partially unsaturated (e.g., cycloalkenyl, cycloalkadienyl, etc.) all carbon ring having 3 to 7 carbon atoms (i.e., (C_3-C_7)carbocycle). The term "carbocycle" or "carbocyclyl" also includes multiple condensed, saturated and partially unsaturated all carbon ring systems (e.g., ring systems comprising 2, 3 or 4 carbocyclic rings). Accordingly, carbocycle includes multicyclic carbocyles such as a bicyclic carbocycles (e.g., bicyclic carbocycles having about 6 to 20 or 6 to 12 carbon atoms such as bicyclo[3.1.0]hexane and bicyclo[2.1.1]hexane), and polycyclic carbocycles (e.g tricyclic and tetracyclic carbocycles with up to about 20 carbon atoms). The rings of the multiple condensed ring system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. For example, multicyclic carbocyles can be connected to each other via a single carbon atom to form a spiro connection (e.g., spiropentane, spiro[4,5]decane, etc), via two adjacent carbon atoms to form a fused connection (e.g., carbocycles such as decahydronaphthalene, norsabinane, norcarane) or via two non-adjacent carbon atoms to form a bridged connection (e.g., norbornane, bicyclo[2.2.2]octane, etc). The "carbocycle" or "carbocyclyl" can also be optionally substituted with one or more (e.g., 1, 2 or 3) oxo groups. In one embodiment the term carbocycle includes a C_{3-12} carbocycle. In one embodiment the term carbocycle includes a C_{3-8} carbocycle. In one embodiment the term carbocycle includes a C_{3-6} carbocycle. In one embodiment the term carbocycle includes a C_{3-5} carbocycle. Non-limiting examples of carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, bicyclo[2.2.1]heptane, pinane, adamantane, norborene, spirocyclic C_{5-12} alkane, and 1-cyclohex-3-enyl. In one embodiment the term "cycloalkyl" refers to a single saturated all carbon ring having 3 to 8 carbon atoms. Non-limiting examples of carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0137] The term "(C_{3-8}cycloalkyl)C_{1-8} alkyl" refers to a (C_{3-8}cycloalkyl) group that is attached through an alkyl group (*e.g.*, cyclopropylmethyl or 2-cyclopropylethyl).

[0138] The term "heteroaryl" as used herein refers to a single aromatic ring that has at least one atom other than carbon in the ring, wherein the atom is selected from the group consisting of oxygen, nitrogen and sulfur; "heteroaryl" also includes multiple condensed ring systems that have at least one such aromatic ring, which multiple condensed ring systems are further described

below. Thus, "heteroaryl" includes single aromatic rings of from about 1 to 6 carbon atoms and about 1-4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur. The sulfur and nitrogen atoms may also be present in an oxidized form provided the ring is aromatic. Exemplary heteroaryl ring systems include but are not limited to pyridyl, pyrimidinyl, oxazolyl or furyl. "Heteroaryl" also includes multiple condensed ring systems (e.g., ring systems comprising 2, 3 or 4 rings) wherein a heteroaryl group, as defined above, is condensed with one or more rings selected from heteroaryls (to form for example a naphthyridinyl such as 1,8-naphthyridinyl), heterocycles, (to form for example a 1, 2, 3, 4-tetrahydronaphthyridinyl such as 1,2,3,4-tetrahydro-1,8-naphthyridinyl), carbocycles (to form for example 5,6,7,8-tetrahydroquinolyl) and aryls (to form for example indazolyl) to form the multiple condensed ring system. Thus, a heteroaryl (a single aromatic ring or multiple condensed ring system) has about 1-20 carbon atoms and about 1-6 heteroatoms within the heteroaryl ring. A heteroaryl (a single aromatic ring or multiple condensed ring system) can also have about 5 to 20 or about 5 to 15 or about 5 to 10 members within the heteroaryl ring. Such multiple condensed ring systems may be optionally substituted with one or more (e.g., 1, 2, 3 or 4) oxo groups on the carbocycle or heterocycle portions of the condensed ring. The rings of the multiple condensed ring system can be connected to each other via fused, spiro and bridged bonds when allowed by valency requirements. It is to be understood that the individual rings of the multiple condensed ring system may be connected in any order relative to one another. It is also to be understood that the point of attachment of a multiple condensed ring system (as defined above for a heteroaryl) can be at any position of the multiple condensed ring system including a heteroaryl, heterocycle, aryl or carbocycle portion of the multiple condensed ring system. It is also to be understood that the point of attachment for a heteroaryl or heteroaryl multiple condensed ring system can be at any suitable atom of the heteroaryl or heteroaryl multiple condensed ring system including a carbon atom and a heteroatom (e.g., a nitrogen). Exemplary heteroaryls include but are not limited to pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, thienyl, indolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, furyl, oxadiazolyl, thiadiazolyl, quinolyl, isoquinolyl, benzothiazolyl, benzoxazolyl, indazolyl, quinoxalyl, quinazolyl, 5,6,7,8-tetrahydroisoquinolinyl benzofuranyl, benzimidazolyl, thianaphthenyl, pyrrolo[2,3-b]pyridinyl, quinazolinyl-4(3H)-one, triazolyl, 4,5,6,7-tetrahydro-1H-indazole and 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclo- penta[1,2-c]pyrazole. In one embodiment the term "heteroaryl" refers to a single aromatic ring containing at least one heteroatom. For example, the term includes 5-membered and 6-membered monocyclic aromatic rings that include one or more heteroatoms. Non-limiting examples of

heteroaryl include but are not limited to pyridyl, furyl, thiazole, pyrimidine, oxazole, and thiadiazole.

[0139] The term "(heteroaryl)C_{1-8} alkyl" refers to a (heteroaryl) group that is attached through an alkyl group (e.g., pyrid-2-ylmethyl or 2-(pyrid-2-yl)ethyl).

[0140] The term "heterocycloalkyl," "heterocyclic," or "heterocycle" refers to a saturated or partially unsaturated ring system radical having from 3-10 ring atoms (e.g., 3-10 membered heterocycloalkyl is a heterocycloalkyl radical with 3-10 ring atoms, a C_{2-9} heterocycloalkyl is a heterocycloalkyl having 3-10 ring atoms with 2-9 ring atoms being carbon) that contain from one to five heteroatoms independently selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, nitrogen atom(s) are optionally quaternized, as ring atoms. Unless otherwise stated, a "heterocycloalkyl," "heterocyclic," or "heterocycle" ring can be a monocyclic, a bicyclic, spirocyclic or a polycylic ring system. Non limiting examples of "heterocycloalkyl," "heterocyclic," or "heterocycle" rings include pyrrolidine, piperidine, N-methylpiperidine, imidazolidine, pyrazolidine, butyrolactam, valerolactam, imidazolidinone, hydantoin, dioxolane, phthalimide, piperidine, pyrimidine-2,4(1H,3H)-dione, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine-S-oxide, thiomorpholine-S,S-oxide, piperazine, pyran, pyridone, 3-pyrroline, thiopyran, pyrone, tetrahydrofuran, tetrhydrothiophene, quinuclidine, tropane, 2-azaspiro[3.3]heptane, (1R,5S)-3-azabicyclo[3.2.1]octane, (1s,4s)-2-azabicyclo[2.2.2]octane, (1R,4R)-2-oxa-5-azabicyclo[2.2.2]octane and the like A "heterocycloalkyl," "heterocyclic," or "heterocycle" group can be attached to the remainder of the molecule through one or more ring carbons or heteroatoms. A "heterocycloalkyl," "heterocyclic," or "heterocycle" can include mono- and poly-halogenated variants thereof.

[0141] The term "(heterocycloalkyl)C_{1-8} alkyl" refers to a (heterocycloalkyl) group that is attached through an alkyl group (e.g., pyrrolidin-2-ylmethyl or 2-(pyrrolidine-2-yl)ethyl)

[0142] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si). The nitrogen and sulfur can be in an oxidized form when feasible.

[0143] As used herein, the term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

[0144] As used herein, the term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

[0145] As used herein a wavy line " ~~~ " that intersects a bond in a chemical structure indicates the point of attachment of the bond that the wavy bond intersects in the chemical structure to the remainder of a molecule.

[0146] "Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers can separate under high resolution analytical procedures such as electrophoresis and chromatography.

[0147] "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

[0148] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley and Sons, Inc., New York, 1994. The compounds of the invention can contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or R and S, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer can also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which can occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

[0149] When a bond in a compound formula herein is drawn in a non-stereochemical manner (e.g. flat), the atom to which the bond is attached includes all stereochemical possibilities. When a bond in a compound formula herein is drawn in a defined stereochemical manner (e.g. bold,

bold-wedge, dashed or dashed-wedge), it is to be understood that the atom to which the stereochemical bond is attached is enriched in the absolute stereoisomer depicted unless otherwise noted. In one embodiment, the compound may be at least 51% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 80% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 90% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 95% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 97% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 98% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 99% the absolute stereoisomer depicted.

[0150] As used herein, the term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

[0151] As used herein, the term "solvate" refers to an association or complex of one or more solvent molecules and a compound of the invention. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, and ethanolamine. The term "hydrate" refers to the complex where the solvent molecule is water.

[0152] As used herein, the term "protecting group" refers to a substituent that is commonly employed to block or protect a particular functional group on a compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBZ) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include acetyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include phenylsulfonylethyl, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(p-toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfenyl)ethyl, 2-(diphenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups

and their use, see P.G.M. Wuts and T.W. Greene, Greene's Protective Groups in Organic Synthesis 4th edition, Wiley-Interscience, New York, 2006.

[0153] As used herein, the term "mammal" includes, but is not limited to, humans, mice, rats, guinea pigs, monkeys, dogs, cats, horses, cows, pigs, and sheep.

[0154] As used herein, the term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S. M., et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0155] The neutral forms of the compounds can be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0156] In addition to salt forms, the present invention provides compounds which are in a prodrug form. As used herein the term "prodrug" refers to those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0157] Prodrugs of the invention include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues, is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of a compound of the present invention. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes phosphoserine, phosphothreonine, phosphotyrosine, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, gamma-carboxyglutamate, hippuric acid, octahydroindole-2-carboxylic acid, statine, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, penicillamine, ornithine, 3-methylhistidine, norvaline, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, methyl-alanine, para-benzoylphenylalanine, phenylglycine, propargylglycine, sarcosine, methionine sulfone and tert-butylglycine.

[0158] Additional types of prodrugs are also encompassed. For instance, a free carboxyl group of a compound of the invention can be derivatized as an amide or alkyl ester. As another example, compounds of this invention comprising free hydroxy groups can be derivatized as prodrugs by converting the hydroxy group into a group such as, but not limited to, a phosphate ester, hemisuccinate, dimethylaminoacetate, or phosphoryloxymethyloxycarbonyl group, as outlined in Fleisher, D. et al., (1996) Improved oral drug delivery: solubility limitations overcome by the use of prodrugs Advanced Drug Delivery Reviews, 19:115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and

(acyloxy)ethyl ethers, wherein the acyl group can be an alkyl ester optionally substituted with groups including, but not limited to, ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in J. Med. Chem., (1996), 39:10. More specific examples include replacement of the hydrogen atom of the alcohol group with a group such as (C_{1-6})alkanoyloxymethyl, 1-((C_{1-6})alkanoyloxy)ethyl, 1-methyl-1-((C_{1-6})alkanoyloxy)ethyl, (C_{1-6})alkoxycarbonyloxymethyl, N-(C_{1-6})alkoxycarbonylaminomethyl, succinoyl, (C_{1-6})alkanoyl, alpha-amino(C_{1-4})alkanoyl, arylacyl and alpha-aminoacyl, or alpha-aminoacyl-alpha-aminoacyl, where each alpha-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, -$P(O)(O(C_{1-6})alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

[0159] For additional examples of prodrug derivatives, see, for example, a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985); b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs," by H. Bundgaard p. 113-191 (1991); c) H. Bundgaard, Advanced Drug Delivery Reviews, 8:1-38 (1992); d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77:285 (1988); and e) N. Kakeya, et al., Chem. Pharm. Bull., 32:692 (1984), each of which is specifically incorporated herein by reference.

[0160] Additionally, the present invention provides for metabolites of compounds of the invention. As used herein, a "metabolite" refers to a product produced through metabolism in the body of a specified compound or salt thereof. Such products can result for example from the oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound.

[0161] Metabolite products typically are identified by preparing a radiolabelled (e.g., ^{14}C or ^{3}H) isotope of a compound of the invention, administering it parenterally in a detectable dose (e.g., greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g., by MS, LC/MS or NMR analysis. In general, analysis

of metabolites is done in the same way as conventional drug metabolism studies well known to those skilled in the art. The metabolite products, so long as they are not otherwise found in vivo, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention.

Pharmaceutical Compositions and Administration

[0162] In addition to one or more of the compounds provided above (or stereoisomers, geometric isomers, tautomers, solvates, metabolites, isotopes, pharmaceutically acceptable salts, or prodrugs thereof), the invention also provides for compositions and medicaments comprising a compound of the invention and at least one pharmaceutically acceptable carrier, diluent or excipient. The compositions of the invention can be used to selectively inhibit NaV1.7 in patients (e.g, humans).

[0163] The term "composition," as used herein, is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0164] In one embodiment, the invention provides for pharmaceutical compositions (or medicaments) comprising a compound as described herein, and its stereoisomers, geometric isomers, tautomers, solvates, metabolites, isotopes, pharmaceutically acceptable salts, or prodrugs thereof) and a pharmaceutically acceptable carrier, diluent or excipient. In another embodiment, the invention provides for preparing compositions (or medicaments) comprising compounds of the invention. In another embodiment, the invention provides for administering a compound of the invention or a and compositions comprising a compound of the invention to a patient (e.g., a human patient) in need thereof.

[0165] Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The effective amount of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to inhibit NaV1.7 activity as required to prevent or treat the

undesired disease or disorder, such as for example, pain. For example, such amount may be below the amount that is toxic to normal cells, or the mammal as a whole.

[0166] In one example, the therapeutically effective amount of the compound of the invention administered parenterally per dose will be in the range of about 0.01-100 mg/kg, alternatively about e.g., 0.1 to 20 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day. The daily does is, in certain embodiments, given as a single daily dose or in divided doses two to six times a day, or in sustained release form. In the case of a 70kg adult human, the total daily dose will generally be from about 7mg to about 1,400mg. This dosage regimen may be adjusted to provide the optimal therapeutic response. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

[0167] The compounds of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

[0168] The compounds of the invention may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, intracerebral, intraocular, intralesional or subcutaneous administration.

[0169] The compositions comprising compounds as described herein or an embodiment thereof are normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. A typical formulation is prepared by mixing a compound of the present invention and a diluent, carrier or excipient. Suitable diluents, carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams and Wilkins, 2004; Gennaro, Alfonso R., et al. Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams and Wilkins, 2000; and Rowe, Raymond C. Handbook of Pharmaceutical Excipients. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating

agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

[0170] Suitable carriers, diluents and excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water and the like. The particular carrier, diluent or excipient used will depend upon the means and purpose for which a compound of the present invention is being applied. Solvents are generally selected based on solvents recognized by persons skilled in the art as safe (GRAS) to be administered to a mammal. In general, safe solvents are non-toxic aqueous solvents such as water and other non-toxic solvents that are soluble or miscible in water. Suitable aqueous solvents include water, ethanol, propylene glycol, polyethylene glycols (e.g., PEG 400, PEG 300), etc. and mixtures thereof. The formulations can also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

[0171] Acceptable diluents, carriers, excipients and stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG). A active pharmaceutical ingredient of the

invention (e.g., a compound or pharmaceutically acceptable salt of the invention) can also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington: The Science and Practice of Pharmacy: Remington the Science and Practice of Pharmacy (2005) 21st Edition, Lippincott Williams and Wilkins, Philidelphia, PA.

[0172] Sustained-release preparations of a compound can be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing a compound as described herein, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinyl alcohol)), polylactides (U.S. Patent No. 3,773,919), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., Biopolymers 22:547, 1983), non-degradable ethylene-vinyl acetate (Langer et al., J. Biomed. Mater. Res. 15:167, 1981), degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate) and poly-D-(-)-3-hydroxybutyric acid (EP 133,988A). Sustained release compositions also include liposomally entrapped compounds, which can be prepared by methods known per se (Epstein et al., Proc. Natl. Acad. Sci. U.S.A. 82:3688, 1985; Hwang et al., *Proc. Natl. Acad. Sci. U.S.A.* 77:4030, 1980; U.S. Patent Nos. 4,485,045 and 4,544,545; and EP 102,324A). Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamelar type in which the lipid content is greater than about 30 mol % cholesterol, the selected proportion being adjusted for the optimal therapy.

[0173] The formulations include those suitable for the administration routes detailed herein. The formulations can conveniently be presented in unit dosage form and can be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington: The Science and Practice of Pharmacy: Remington the Science and Practice of Pharmacy (2005) 21st Edition, Lippincott Williams and Wilkins, Philidelphia, PA. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients.

[0174] In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers, diluents or excipients or finely divided solid carriers, diluents or excipients, or both, and then, if necessary, shaping the product. A typical formulation is prepared by mixing a compound of the present invention and a carrier, diluent or excipient. The formulations can be prepared using conventional dissolution and mixing procedures. For example, the bulk drug substance (i.e., compound of the present invention or stabilized form of the compound (e.g., complex with a cyclodextrin derivative or other known complexation agent) is dissolved in a suitable solvent in the presence of one or more of the excipients described above. A compound of the present invention is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to enable patient compliance with the prescribed regimen.

[0175] In one example, compounds as described herein may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but preferably ranges anywhere from about 3 to about 8. In one example, a compound of of the invention is formulated in an acetate buffer, at pH 5. In another embodiment, a compound of the invention is sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

[0176] Formulations of a compound as described herein suitable for oral administration can be prepared as discrete units such as pills, capsules, cachets or tablets each containing a predetermined amount of a compound of the invention.

[0177] Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets can optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

[0178] Tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, e.g., gelatin capsules, syrups or elixirs can be prepared for oral use. Formulations of a compound as described herein intended for oral use can be

prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients can be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets can be uncoated or can be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax can be employed.

[0179] An example of a suitable oral administration form is a tablet containing about 1 mg, 5 mg, 10 mg, 25mg, 30mg, 50mg, 80mg, 100mg, 150mg, 250mg, 300mg and 500mg of the compound of the invention compounded with about 90-30mg anhydrous lactose, about 5-40mg sodium croscarmellose, about 5-30mg polyvinylpyrrolidone (PVP) K30, and about 1-10mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An example of an aerosol formulation can be prepared by dissolving the compound, for example 5-400mg, of the invention in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier, e.g. a salt such sodium chloride, if desired. The solution may be filtered, e.g., using a 0.2 micron filter, to remove impurities and contaminants.

[0180] For treatment of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w. When formulated in an ointment, the active ingredient can be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients can be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base can include a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations can desirably include a compound which enhances absorption or penetration of the

active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulfoxide and related analogs.

[0181] The oily phase of the emulsions of this invention can be constituted from known ingredients in a known manner. While the phase can comprise merely an emulsifier, it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

[0182] In one aspect of topical applications, it is desired to administer an effective amount of a pharmaceutical composition according to the invention to target area, e.g., skin surfaces, mucous membranes, and the like, which are adjacent to peripheral neurons which are to be treated. This amount will generally range from about 0.0001 mg to about 1 g of a compound of the invention per application, depending upon the area to be treated, whether the use is diagnostic, prophylactic or therapeutic, the severity of the symptoms, and the nature of the topical vehicle employed. A preferred topical preparation is an ointment, wherein about 0.001 to about 50 mg of active ingredient is used per cc of ointment base. The pharmaceutical composition can be formulated as transdermal compositions or transdermal delivery devices ("patches"). Such compositions include, for example, a backing, active compound reservoir, a control membrane, liner and contact adhesive. Such transdermal patches may be used to provide continuous pulsatile, or on demand delivery of the compounds of the present invention as desired.

[0183] Aqueous suspensions of a compound as described herein contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, croscarmellose, povidone, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene

oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension can also contain one or more preservatives such as ethyl or *n*-propyl *p*-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

[0184] Formulations of a compound as described herein can be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butanediol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables.

[0185] The amount of active ingredient that can be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans can contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which can vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion can contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

[0186] Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which can contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which can include suspending agents and thickening agents.

[0187] Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations

in a concentration of about 0.5 to 20% w/w, for example about 0.5 to 10% w/w, for example about 1.5% w/w.

[0188] Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0189] Formulations for rectal administration can be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

[0190] Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration can be prepared according to conventional methods and can be delivered with other therapeutic agents such as compounds heretofore used in the treatment of disorders as described below.

[0191] The formulations can be packaged in unit-dose or multi-dose containers, for example sealed ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water, for injection immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

[0192] When the binding target is located in the brain, certain embodiments of the invention provide for a compound as described herein to traverse the blood-brain barrier. Certain neurodegenerative diseases are associated with an increase in permeability of the blood-brain barrier, such that a compound of of the invention can be readily introduced to the brain. When the blood-brain barrier remains intact, several art-known approaches exist for transporting molecules across it, including, but not limited to, physical methods, lipid-based methods, and receptor and channel-based methods.

[0193] Physical methods of transporting a compound as described herein across the blood-brain barrier include, but are not limited to, circumventing the blood- brain barrier entirely, or by creating openings in the blood-brain barrier.

[0194] Circumvention methods include, but are not limited to, direct injection into the brain (see, e.g., Papanastassiou et al., Gene Therapy 9:398-406, 2002), interstitial infusion/convection-enhanced delivery (see, e.g., Bobo et al., Proc. Natl. Acad. Sci. U.S.A. 91 :2076-2080, 1994), and implanting a delivery device in the brain (see, e.g., Gill et al., Nature Med. 9:589-595, 2003; and Gliadel Wafers™, Guildford Pharmaceutical). Methods of creating openings in the barrier include, but are not limited to, ultrasound (see, e.g., U.S. Patent Publication No. 2002/0038086), osmotic pressure (e.g., by administration of hypertonic mannitol (Neuwelt, E. A., Implication of the Blood-Brain Barrier and its Manipulation, Volumes 1 and 2, Plenum Press, N.Y., 1989)), and permeabilization by, e.g., bradykinin or permeabilizer A-7 (see, e.g., U.S. Patent Nos. 5,112,596, 5,268,164, 5,506,206, and 5,686,416).

[0195] Lipid-based methods of transporting a compound as described herein across the blood-brain barrier include, but are not limited to, encapsulating the a compound as described herein in liposomes that are coupled to antibody binding fragments that bind to receptors on the vascular endothelium of the blood- brain barrier (see, e.g., U.S. Patent Application Publication No. 2002/0025313), and coating a compound as described herein in low-density lipoprotein particles (see, e.g., U.S. Patent Application Publication No. 2004/0204354) or apolipoprotein E (see, e.g., U.S. Patent Application Publication No. 2004/0131692).

[0196] Receptor and channel-based methods of transporting a compound as described herein across the blood-brain barrier include, but are not limited to, using glucocorticoid blockers to increase permeability of the blood-brain barrier (see, e.g., U.S. Patent Application Publication Nos. 2002/0065259, 2003/0162695, and 2005/0124533); activating potassium channels (see, e.g., U.S. Patent Application Publication No. 2005/0089473), inhibiting ABC drug transporters (see, e.g., U.S. Patent Application Publication No. 2003/0073713); coating a compound as described herein with a transferrin and modulating activity of the one or more transferrin receptors (see, e.g., U.S. Patent Application Publication No. 2003/0129186), and cationizing the antibodies (see, e.g., U.S. Patent No. 5,004,697).

[0197] For intracerebral use, in certain embodiments, the compounds can be administered continuously by infusion into the fluid reservoirs of the CNS, although bolus injection may be acceptable. The inhibitors can be administered into the ventricles of the brain or otherwise

introduced into the CNS or spinal fluid. Administration can be performed by use of an indwelling catheter and a continuous administration means such as a pump, or it can be administered by implantation, e.g., intracerebral implantation of a sustained-release vehicle. More specifically, the inhibitors can be injected through chronically implanted cannulas or chronically infused with the help of osmotic minipumps. Subcutaneous pumps are available that deliver proteins through a small tubing to the cerebral ventricles. Highly sophisticated pumps can be refilled through the skin and their delivery rate can be set without surgical intervention. Examples of suitable administration protocols and delivery systems involving a subcutaneous pump device or continuous intracerebroventricular infusion through a totally implanted drug delivery system are those used for the administration of dopamine, dopamine agonists, and cholinergic agonists to Alzheimer's disease patients and animal models for Parkinson's disease, as described by Harbaugh, *J. Neural Transm. Suppl*. 24:271, 1987; and DeYebenes et al, Mov. Disord. 2: 143, 1987.

[0198] A compound as described herein used in the invention are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. A compound as described herein need not be, but is optionally formulated with one or more agent currently used to prevent or treat the disorder in question. The effective amount of such other agents depends on the amount of a compound of the invention present in the formulation, the type of disorder or treatment, and other factors discussed above.

[0199] These are generally used in the same dosages and with administration routes as described herein, or about from 1 to 99% of the dosages described herein, or in any dosage and by any route that is empirically/clinically determined to be appropriate.

[0200] For the prevention or treatment of disease, the appropriate dosage of a compound as described herein (when used alone or in combination with other agents) will depend on the type of disease to be treated, the properties of the compound, the severity and course of the disease, whether the compound is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the compound, and the discretion of the attending physician. The compound is suitably administered to the patient at one time or over a series of treatments. Depending on the type and severity of the disease, about 1 μg/kg to 15 mg/kg (e.g., 0.1 mg/kg-10 mg/kg) of compound can be an initial candidate dosage for administration to the

patient, whether, for example, by one or more separate administrations, or by continuous infusion. One typical daily dosage might range from about 1 μg kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment would generally be sustained until a desired suppression of disease symptoms occurs. One exemplary dosage of a compound of the invention would be in the range from about 0.05 mg/kg to about 10 mg/kg. Thus, one or more doses of about 0.5 mg/kg, 2.0 mg/kg, 4.0 mg/kg, or 10 mg/kg (or any combination thereof) may be administered to the patient. Such doses may be administered intermittently, e.g., every week or every three weeks (e.g., such that the patient receives from about two to about twenty, or, e.g., about six doses of the antibody). An initial higher loading dose, followed by one or more lower doses may be administered. An exemplary dosing regimen comprises administering an initial loading dose of about 4 mg/kg, followed by a weekly maintenance dose of about 2 mg kg of the compound. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

[0201] Other typical daily dosages might range from, for example, about 1 g/kg to up to 100 mg/kg or more (e.g., about 1 μg kg to 1 mg/kg, about 1 μg/kg to about 5 mg/kg, about 1 mg kg to 10 mg/kg, about 5 mg/kg to about 200 mg/kg, about 50 mg/kg to about 150 mg/mg, about 100 mg/kg to about 500 mg/kg, about 100 mg/kg to about 400 mg/kg, and about 200 mg/kg to about 400 mg/kg), depending on the factors mentioned above. Typically, the clinician will administer a compound until a dosage is reached that results in improvement in or, optimally, elimination of, one or more symptoms of the treated disease or condition. The progress of this therapy is easily monitored by conventional assays. One or more agent provided herein may be administered together or at different times (e.g., one agent is administered prior to the administration of a second agent). One or more agent may be administered to a subject using different techniques (e.g., one agent may be administered orally, while a second agent is administered via intramuscular injection or intranasally). One or more agent may be administered such that the one or more agent has a pharmacologic effect in a subject at the same time. Alternatively, one or more agent may be administered, such that the pharmacological activity of the first administered agent is expired prior the administration of one or more secondarily administered agents (e.g., 1, 2, 3, or 4 secondarily administered agents).

Synthesis of Compounds

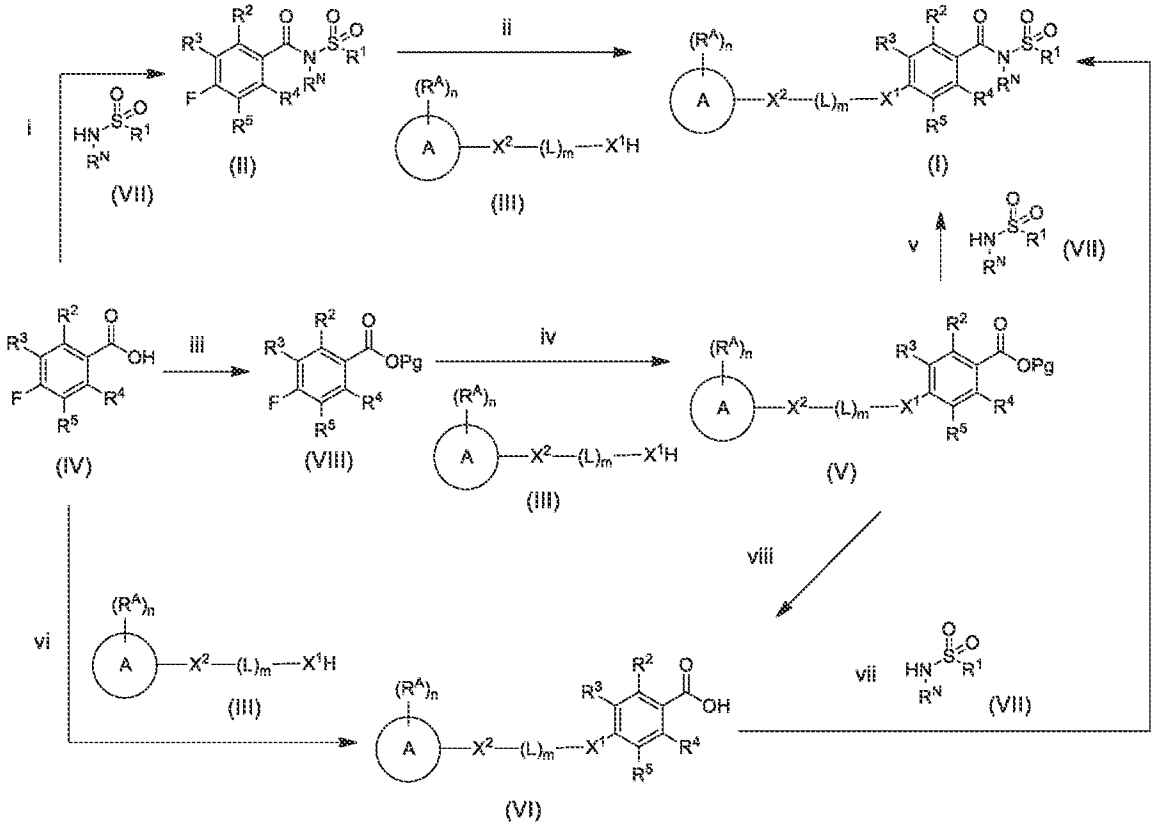
[0202] Compounds of formula I, II, and III can be prepared using starting materials, synthetic processes and synthetic intermediates like those described in the Examples below. In particular,

compounds of formula I can be prepared as illustrated in Schemes 1 and 2; compounds of formula II can be prepared as illustrated in Scheme 3; and compounds of formula III can be prepared as illustrated in Schemes 4 and 5.

[0203] Compounds of formula (I), wherein X^1 is O, S, or NH, may be prepared by the process illustrated in Scheme 1.

[0204] Compounds of formula (I) can be made from compounds of formula (II) by displacement with formula (III) and a base (reaction step ii in Scheme 1). Suitable conditions include potassium *tert*-butoxide in DMSO, NaH in DMF or K_2CO_3 in DMF. Formula (II) can be made according to step (i) by activation of the acid group of formula (IV) with reagents such as oxalyl chloride, carbonyl di-imidazole (CDI), propylphosphonic anhydride, a uronium based amide coupling agent or a carbodiimide reagent followed by displacement with a sulfonamide of formula (VII) in the presence of a nucleophilic base such as 4-dimethylaminopyridine. Illustrative conditions comprise *N*, *N*-dimethylaminopropyl-*N'*-ethylcarbodiimide and 4-dimethylaminopyridine with *N*, *N*-diisopropylethylamine.

Scheme 1 – Synthesis of compounds of formula I

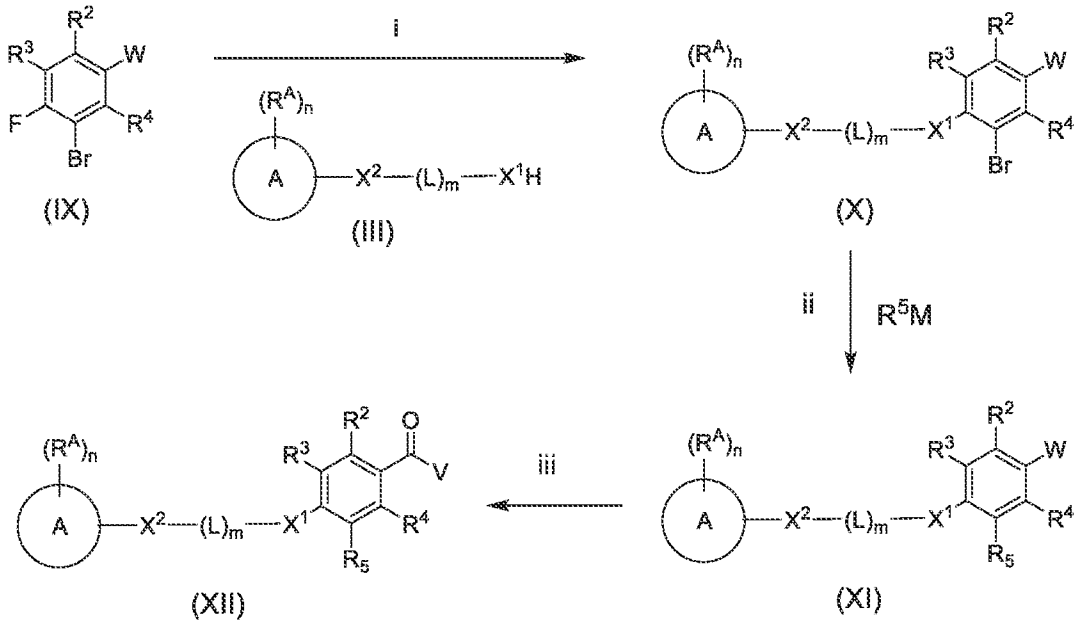


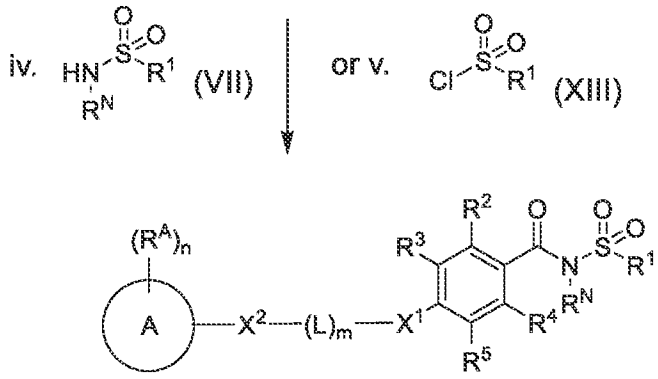
[0205] Alternatively, compounds of formula (I) can be made from compounds of formula (IV) by reversing steps (i) and (ii) as described in Scheme 1. Illustrative conditions for steps vi and vii are as previously described in steps (ii) and (i), respectively.

[0206] Compounds of formula (I) can also be made from compounds of formula (V) according to step (v) by displacement of the ester with compounds of formula (VII) and a suitable base such as potassium *tert*-butoxide, NaH or DBU. Compounds of formula (I) can also be made from compounds of formula (v) by a two steps sequence (see steps viii and vii in Scheme 1). Compounds of formula (V) can be made from compounds of formula (VIII) according to step (iv) via a nucleophilic substitution reaction using compounds of formula (III) and a base as described in step ii. Compounds of formula (VIII) can be made from compounds of formula (IV) according to step (iii) using protecting group methodology as described in references such as 'Greene's Protective Groups in Organic Synthesis'. When Pg is tolyl, illustrative conditions comprise thionyl chloride or carbonyldiimidazole with para-cresol. When Pg is *tert*-butyl, illustrative conditions comprise di-*tert* butyl dicarbonate and 4-dimethylaminopyridine in *tert*-butanol.

[0207] Compounds of formula (I), wherein R^5 is Ar, heteroaryl, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-10} cycloalkyl or C_{2-9} heterocycloalkyl can be prepared by the process illustrated in Scheme 2. In certain embodiment, W groups in compounds of formula (IX, X and XI) are an ester or cyano group.

Scheme 2 – Synthesis of compounds of formula I





(I)

[0208] Compounds of formula (I) can be prepared from compounds of formulae (XII) (-V = OH) according to reaction step (iv) by activation of the acid group with reagents such as oxalyl chloride, carbonyl di-imidazole (CDI), a uronium based amide coupling agent, propylphosphonic anhydride or a carbodiimide reagent followed by displacement with a suitable sulfonamide of formula (VII) in the presence of a nucleophilic base such as 4-dimethylaminopyridine.

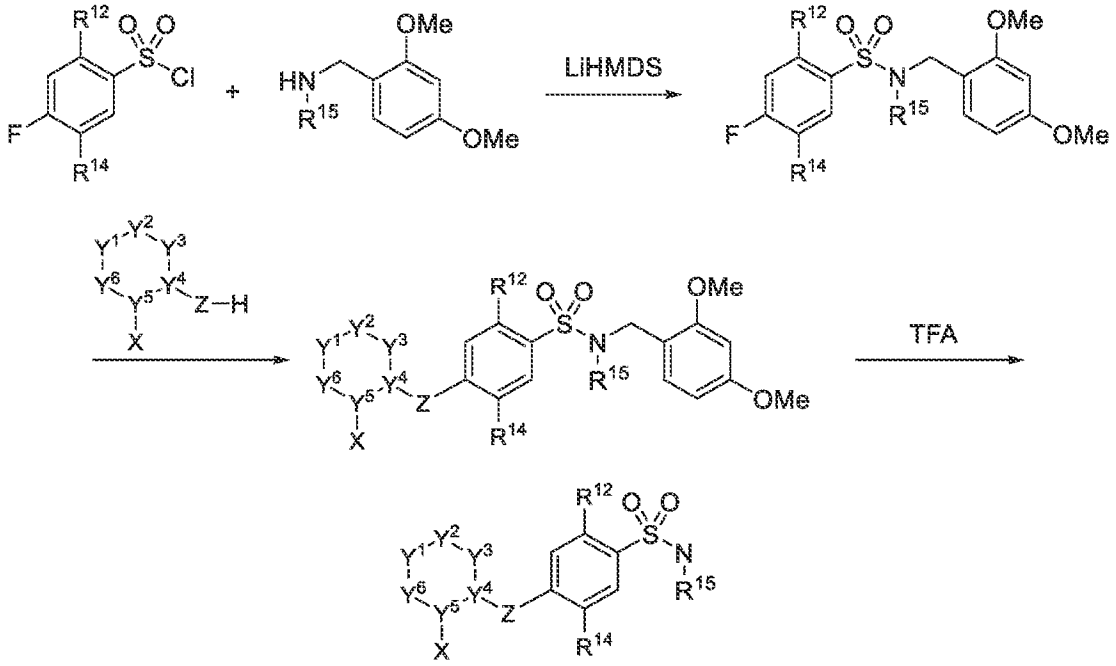
[0209] Alternatively, compounds of formula (I) can be prepared from compounds of formula (XII) (-V = NH_2) according to reaction step (v) by displacement of a sulfonyl chloride of formula (XIII) under basic reaction conditions.

[0210] Compounds of formula (XII) can be prepared by hydrolysis of the nitrile functional group in compounds of formula (XI, W = CN) or by hydrolysis of the ester functional group in compounds of formula (XI, W = CO_2Pg) by either acidic or basic methods according to step (iii) as required.

[0211] Compounds of formula (XI) can be prepared from compounds of formula (X) by palladium-catalyzed coupling of a compound of formula (R_5M) according to step (ii).

[0212] Conveniently the coupling is effective with a boronic acid or ester of formula (R_5M). The coupling reaction can be carried out with a variety of palladium catalysts such as palladium acetate or tetrakistriphenylphosphine palladium (0) in various solvents and in the presence of bases such as sodium and potassium carbonate, cesium fluoride or potassium phosphate. Compounds of formula (X) can be prepared under similar conditions as described for the preparation of compounds of formula (V), (VI) and (I) in Scheme 1.

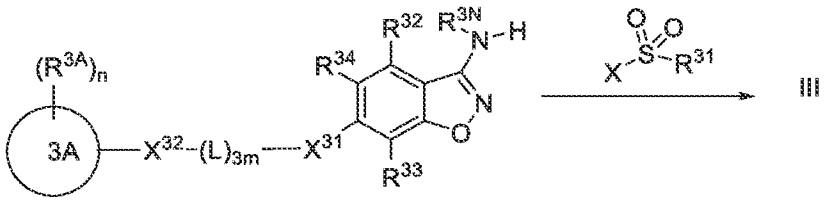
Scheme 3 – Synthesis of compounds of formula II



[0213] Compounds of formula III may be prepared by the processes illustrated in Scheme 4.

[0214] A compound of Formula III can be prepared by treating an amine of Formula IIIa with a sulfonylating reagent, e.g., a reagent of formula X-SO_2-R^{31} wherein X is a suitable leaving group, such as chloro, to provide the compound of Formula I. Accordingly, the invention also provides novel amines of Formula IIIa, which are useful intermediates for preparing the corresponding sulfonamides of Formula III. The invention also provides a method for preparing a compound of Formula III comprising treating a corresponding amine of Formula IIIa with corresponding sulfonylating reagent to provide the compound of Formula III.

Scheme 4 – Synthesis of compounds of formula III



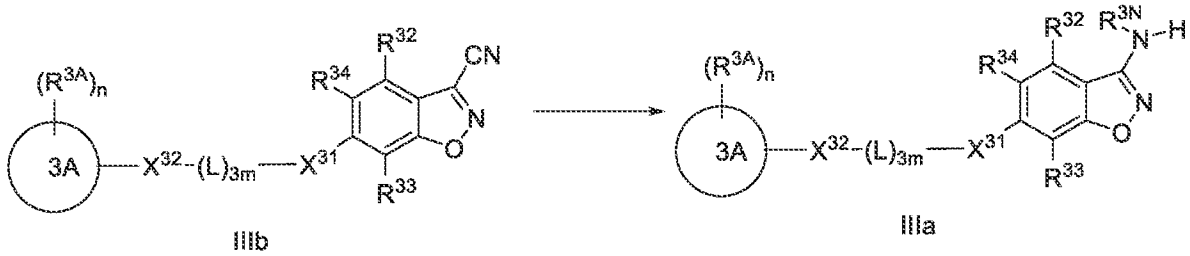
(IIIa)

[0215] An intermediate amine of Formula IIIa wherein R^N is H can be prepared by treating a cyano fluoride of Formula IIIb with N-hydroxyacetamide as illustrated in Scheme 5.

[0216] Amines of Formula IIIa wherein R^N is H are general intermediates that can be converted to compounds of formula III using standard techniques. Accordingly, the invention also provides novel amines of Formula IIIa wherein R^N is H as well as novel compounds of

Formula IIIb, which are useful intermediates for preparing the corresponding sulfonamides of Formula III. The invention also provides a method for preparing a compound of Formula IIIa, wherein R^N is H comprising treating a corresponding amine of Formula IIIb with N-hydroxyacetamide to provide the compound of Formula IIIa.

[0217] Scheme 5 – Preparation of Compound IIIa



Indications and Methods of Treatment

[0218] The compounds of the invention modulate, preferably inhibit, ion flux through a voltage-dependent sodium channel in a mammal, (e.g, a human). Any such modulation, whether it be partial or complete inhibition or prevention of ion flux, is sometimes referred to herein as "blocking" and corresponding compounds as "blockers" or "inhibitors". In general, the compounds of the invention modulate the activity of a sodium channel downwards by inhibiting the voltage-dependent activity of the sodium channel, and/or reduce or prevent sodium ion flux across a cell membrane by preventing sodium channel activity such as ion flux.

[0219] Accordingly, the compounds of the invention are sodium channel blockers and are therefore useful for treating diseases and conditions in mammals, for example humans, and other organisms, including all those diseases and conditions which are the result of aberrant voltage-dependent sodium channel biological activity or which may be ameliorated by modulation of voltage-dependent sodium channel biological activity. In particular, the compounds of the invention, i.e., the compounds of formula (I) and embodiments and (or stereoisomers, geometric isomers, tautomers, solvates, metabolites, isotopes, pharmaceutically acceptable salts, or prodrugs thereof), are useful for treating diseases and conditions in mammals, for example humans, which are the result of aberrant voltage-dependent NaV1.7 biological activity or which may be ameliorated by the modulation, preferably the inhibition, of NaV1.7 biological activity. In certain aspects, the compounds of the invention selectively inhibit NaV1.7 over NaV1.5.

[0220] As defined herein, a sodium channel-mediated disease or condition refers to a disease or condition in a mammal, preferably a human, which is ameliorated upon modulation of the

sodium channel and includes, but is not limited to, pain, central nervous conditions such as epilepsy, anxiety, depression and bipolar disease; cardiovascular conditions such as arrhythmias, atrial fibrillation and ventricular fibrillation; neuromuscular conditions such as restless leg syndrome and muscle paralysis or tetanus; neuroprotection against stroke, neural trauma and multiple sclerosis; and channelopathies such as erythromyalgia and familial rectal pain syndrome.

[0221] In one aspect, the present invention relates to compounds, pharmaceutical compositions and methods of using the compounds and pharmaceutical compositions for the treatment of sodium channel-mediated diseases in mammals, preferably humans and preferably diseases and conditions related to pain, central nervous conditions such as epilepsy, anxiety, depression and bipolar disease; cardiovascular conditions such as arrhythmias, atrial fibrillation and ventricular fibrillation; neuromuscular conditions such as restless leg syndrome and muscle paralysis or tetanus; neuroprotection against stroke, neural trauma and multiple sclerosis; and channelopathies such as erythromyalgia and familial rectal pain syndrome, by administering to a mammal, for example a human, in need of such treatment an effective amount of a sodium channel blocker modulating, especially inhibiting, agent.

[0222] A sodium channel-mediated disease or condition also includes pain associated with HIV, HIV treatment induced neuropathy, trigeminal neuralgia, glossopharyngeal neuralgia, neuropathy secondary to metastatic infiltration, adiposis dolorosa, thalamic lesions, hypertension, autoimmune disease, asthma, drug addiction (e.g., opiate, benzodiazepine, amphetamine, cocaine, alcohol, butane inhalation), Alzheimer, dementia, age-related memory impairment, Korsakoff syndrome, restenosis, urinary dysfunction, incontinence, Parkinson's disease, cerebrovascular ischemia, neurosis, gastrointestinal disease, sickle cell anemia, transplant rejection, heart failure, myocardial infarction, reperfusion injury, intermittant claudication, angina, convulsion, respiratory disorders, cerebral or myocardial ischemias, long-QT syndrome, Catecholeminergic polymorphic ventricular tachycardia, ophthalmic diseases, spasticity, spastic paraplegia, myopathies, myasthenia gravis, paramyotonia congentia, hyperkalemic periodic paralysis, hypokalemic periodic paralysis, alopecia, anxiety disorders, psychotic disorders, mania, paranoia, seasonal affective disorder, panic disorder, obsessive compulsive disorder (OCD), phobias, autism, Aspergers Syndrome, Retts syndrome, disintegrative disorder, attention deficit disorder, aggressivity, impulse control disorders, thrombosis, pre clampsia, congestive cardiac failure, cardiac arrest, Freidrich's ataxia, Spinocerebellear ataxia, myelopathy, radiculopathy, systemic lupus erythamatosis, granulomatous disease, olivo-ponto-cerebellar atrophy, spinocerebellar ataxia, episodic ataxia, myokymia, progressive pallidal atrophy, progressive supranuclear palsy

and spasticity, traumatic brain injury, cerebral oedema, hydrocephalus injury, spinal cord injury, anorexia nervosa, bulimia, Prader-Willi syndrome, obesity, optic neuritis, cataract, retinal haemorrhage, ischaemic retinopathy, retinitis pigmentosa, acute and chronic glaucoma, macular degeneration, retinal artery occlusion, Chorea, Huntington's chorea, cerebral edema, proctitis, post-herpetic neuralgia, eudynia, heat sensitivity, sarcoidosis, irritable bowel syndrome, Tourette syndrome, Lesch-Nyhan Syndrome, Brugado syndrome, Liddle syndrome, Crohns disease, multiple sclerosis and the pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), disseminated sclerosis, diabetic neuropathy, peripheral neuropathy, charcot marie tooth syndrome, arthritic, rheumatoid arthritis, osteoarthritis, chondrocalcinosis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, myotonic dystrophy, muscular dystrophy, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, mental handicap, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxin related illnesses, familial erythromelalgia, primary erythromelalgia, rectal pain, cancer, epilepsy, partial and general tonic seizures, febrile seizures, absence seizures (petit mal), myoclonic seizures, atonic seizures, clonic seizures, Lennox Gastaut, West Syndome (infantile spasms), multiresistant seizures, seizure prophylaxis (anti-epileptogenic), familial Mediterranean fever syndrome, gout, restless leg syndrome, arrhythmias, fibromyalgia, neuroprotection under ischaemic conditions caused by stroke or neural trauma, tachy-arrhythmias, atrial fibrillation and ventricular fibrillation and as a general or local anaesthetic.

[0223] As used herein, the term "pain" refers to all categories of pain and is recognized to include, but is not limited to, neuropathic pain, inflammatory pain, nociceptive pain, idiopathic pain, neuralgic pain, orofacial pain, burn pain, burning mouth syndrome, somatic pain, visceral pain, myofacial pain, dental pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, chronic regional pain syndrome (CRPS),reflex sympathetic dystrophy, brachial plexus avulsion, neurogenic bladder, acute pain (e.g., musculoskeletal and post-operative pain), chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, familial hemiplegic migraine, conditions associated with cephalic pain, sinus headache, tension headache, phantom limb pain, peripheral nerve injury, pain following stroke, thalamic lesions, radiculopathy, HIV pain, post-herpetic pain, non-cardiac chest pain, irritable bowel syndrome and pain associated with bowel disorders and dyspepsia, and combinations thereof.

[0224] Furthermore, sodium channel blockers have clinical uses in addition to pain. The present invention therefore also relates to compounds, pharmaceutical compositions and methods

of using the compounds and pharmaceutical compositions for the treatment of diseases or conditions such as cancer and pruritus (itch).

[0225] Pruritus, commonly known as itch, is a common dermatological condition. While the exact causes of pruritus are complex and incompletely understood, there has long been evidence that itch involves sensory neurons, especially C fibers, similar to those that mediate pain (Schmelz, M., et al., J. Neurosci. (1997), 17: 8003-8). In particular, it is believed that sodium influx through voltage-gated sodium channels is essential for the propagation of itch sensation from the skin. Transmission of the itch impulses results in the unpleasant sensation that elicits the desire or reflex to scratch.

[0226] Multiple causes and electrical pathways for eliciting itch are known. In humans, pruritus can be elicited by histamine or PAR-2 agonists such as mucunain that activate distinct populations of C fibers (Namer, B., et al., J. Neurophysiol. (2008),100: 2062-9). A variety of neurotrophic peptides are known to mediate itch in animal models (Wang, H., and Yosipovitch, G., International Journal of Dermatology (2010), 49: 1-11). Itch can also be elicited by opioids, evidence of distinct pharmacology from that of pain responses.

[0227] There exists a complex interaction between itch and pain responses that arises in part from the overlapping sensory input from the skin (Ikoma, A., et al., Arch. Dermatol. (2003),139: 1475-8) and also from the diverse etiology of both pain and pruritus. Pain responses can exacerbate itching by enhancing central sensitization or lead to inhibition of painful scratching. Particularly severe forms of chronic itch occur when pain responses are absent, as in the case of post-herpetic itch (Oaklander, A.L. , et al., Pain (2002), 96: 9-12).

[0228] The compounds of the invention can also be useful for treating pruritus. The rationale for treating itch with inhibitors of voltage-gated sodium channels, especially NaV1.7, is as follows.

[0229] The propagation of electrical activity in the C fibers that sense pruritinergic stimulants requires sodium entry through voltage-gated sodium channels.

[0230] NaV1.7 is expressed in the C fibers and kerotinocytes in human skin (Zhao, P., et al., Pain (2008), 139: 90-105).

[0231] A gain of function mutation of NaV1.7 (L858F) that causes erythromelalgia also causes chronic itch (Li, Y., et al., Clinical and Experimental Dermatology (2009), 34: e313-e4).

[0232] Chronic itch can be alleviated with treatment by sodium channel blockers, such as the local anesthetic lidocaine (Oaklander, A.L., et al., Pain (2002), 96: 9-12; Villamil, A.G., et al., The American Journal of Medicine (2005), 118: 1160-3). In these reports, lidocaine was effective when administered either intravenously or topically (a Lidoderm patch). Lidocaine can have multiple activities at the plasma concentrations achieved when administered systemically, but when administered topically, the plasma concentrations are only about 1 μM (Center for Drug Evaluation and Research NDA 20-612). At these concentrations, lidocaine is selective for sodium channel block and inhibits spontaneous electrical activity in C fibers and pain responses in animal models (Xiao, W.H., and Bennett, G.J.. Pain (2008), 137: 218-28). The types of itch or skin irritation, include, but are not limited to:

psoriatic pruritus, itch due to hemodyalisis, aguagenic pruritus, and itching caused by skin disorders (e.g., contact dermatitis), systemic disorders, neuropathy, psychogenic factors or a mixture thereof;
itch caused by allergic reactions, insect bites, hypersensitivity (e.g., dry skin, acne, eczema, psoriasis), inflammatory conditions or injury;
itch associated with vulvar vestibulitis; and
skin irritation or inflammatory effect from administration of another therapeutic such as, for example, antibiotics, antivirals and antihistamines.

[0233] The compounds of the invention are also useful in treating certain cancers, such as hormone sensitive cancers, such as prostate cancer (adenocarcinoma), breast cancer, ovarian cancer, testicular cancer and thyroid neoplasia, in a mammal, preferably a human. The voltage gated sodium channels have been demonstrated to be expressed in prostate and breast cancer cells. Up-regulation of neonatal NaV1.5 occurs as an integral part of the metastatic process in human breast cancer and could serve both as a novel marker of the metastatic phenotype and a therapeutic target (Clin. Cancer Res. (2005), Aug. 1; 11(15): 5381-9). Functional expression of voltage-gated sodium channel alpha-subunits, specifically NaV1.7, is associated with strong metastatic potential in prostate cancer (CaP) in vitro. Voltage-gated sodium channel alpha-subunits immunostaining, using antibodies specific to the sodium channel alpha subunit was evident in prostatic tissues and markedly stronger in CaP vs non-CaP patients (Prostate Cancer Prostatic Dis., 2005; 8(3):266-73). See also Diss, J.K.J., et al., Mol. Cell. Neurosci. (2008), 37:537–547 and Kis-Toth, K., et al., The Journal of Immunology (2011), 187:1273–1280.

[0234] In consideration of the above, in one embodiment, the present invention provides a method for treating a mammal for, or protecting a mammal from developing, a sodium channel-

mediated disease, especially pain, comprising administering to the mammal, especially a human, in need thereof, a therapeutically effective amount of a compound of the invention or a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention wherein the compound modulates the activity of one or more voltage-dependent sodium channels.

[0235] In another embodiment of the invention is a method of treating a disease or a condition in a mammal, preferably a human, wherein the disease or condition is selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, and combinations thereof, and wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of an embodiment of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

[0236] One embodiment of this embodiment is wherein the disease or condition is selected from the group consisting of acute pain, chronic pain, neuropathic pain, inflammatory pain, visceral pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post surgical pain, childbirth pain, labor pain, neurogenic bladder, ulcerative colitis, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, peripheral nerve injury, and combinations thereof.

[0237] Another embodiment of this embodiment is wherein the disease or condition is selected from the group consisting of pain associated with HIV, HIV treatment induced neuropathy, trigeminal neuralgia, post herpetic neuralgia, eudynia, heat sensitivity, tosarcoidosis, irritable bowel syndrome, Crohns disease, pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), diabetic neuropathy, peripheral neuropathy, arthritic, rheumatoid arthritis, osteoarthritis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxin related illnesses, familial erythromelalgia, primary erythromelalgia, familial rectal pain, cancer, epilepsy, partial and general tonic seizures, restless leg syndrome, arrhythmias, fibromyalgia,

neuroprotection under ischaemic conditions caused by stroke or neural trauma, tachy arrhythmias, atrial fibrillation and ventricular fibrillation.

[0238] Another embodiment of the invention is a method of treating, but not preventing, pain in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

[0239] One embodiment of this embodiment is a method wherein the pain is selected from the group consisting of neuropathic pain, inflammatory pain, visceral pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post surgical pain, childbirth pain, labor pain, dental pain, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, peripheral nerve injury, trigeminal neuralgia, post herpetic neuralgia, eudynia, familial erythromelalgia, primary erythromelalgia, familial rectal pain or fibromyalgia, and combinations thereof.

[0240] Another embodiment of this embodiment is a method wherein the pain is associated with a disease or condition selected from HIV, HIV treatment induced neuropathy, heat sensitivity, tosarcoidosis, irritable bowel syndrome, Crohns disease, multiple sclerosis, amyotrophic lateral sclerosis, diabetic neuropathy, peripheral neuropathy, rheumatoid arthritis, osteoarthritis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxin related illnesses, neurogenic bladder, ulcerative colitis, cancer, epilepsy, partial and general tonic seizures, restless leg syndrome, arrhythmias, ischaemic conditions caused by stroke or neural trauma, tachy arrhythmias, atrial fibrillation and ventricular fibrillation.

[0241] Another embodiment of the invention is the method of treating pain in a mammal, preferably a human, by the inhibition of ion flux through a voltage dependent sodium channel in the mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of an embodiment of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a

pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

[0242] Another embodiment of the invention is the method of treating pruritus in a mammal, preferably a human, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of an embodiment of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

[0243] Another embodiment of the invention is the method of treating cancer in a mammal, preferably a human, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of an embodiment of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable excipient.

[0244] Another embodiment of the invention is the method of decreasing ion flux through a voltage dependent sodium channel in a cell in a mammal, wherein the method comprises contacting the cell with an embodiment of a compound of the invention, as set forth above, as a stereoisomer, enantiomer or tautomer thereof or mixtures thereof, or a pharmaceutically acceptable salt, solvate or prodrug thereof.

[0245] Another embodiment of the invention is the method of selectively inhibiting a first voltage-gated sodium channel over a second voltage-gated sodium channel in a mammal, wherein the method comprises administering to the mammal an inhibitory amount of a compound of formula (I), or an embodiment of a compound of formula (I).

[0246] Another embodiment of the invention is the method of selectively inhibiting NaV1.7 in a mammal or a mammalian cell as compared to NaV1.5, wherein the method comprises

administering to the mammal in need thereof an inhibitory amount of a compound of formula (I) or an embodiment of an embodiment thereof.

[0247] For each of the above embodiments described related to treating diseases and conditions in a mammal, the present invention also contemplates relatedly a compound as described herein for the use as a medicament in the treatment of such diseases and conditions.

[0248] For each of the above embodiments described related to treating diseases and conditions in a mammal, the present invention also contemplates relatedly the use of a compound as described herein for the manufacture of a medicament for the treatment of such diseases and conditions.

[0249] Another embodiment of the invention is a method of using a compound as described herein as a standard or control in *in vitro* or *in vivo* assays in determining the efficacy of test compounds in modulating voltage-dependent sodium channels.

[0250] In another embodiment of the invention, the compounds as described herein are isotopically-labeled by having one or more atoms therein replaced by an atom having a different atomic mass or mass number. Such isotopically-labeled (i.e., radiolabelled) compounds are considered to be within the scope of this invention. Examples of isotopes that can be incorporated into the compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine, and iodine, such as, but not limited to, ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. These isotopically-labeled compounds would be useful to help determine or measure the effectiveness of the compounds, by characterizing, for example, the site or mode of action on the sodium channels, or binding affinity to pharmacologically important site of action on the sodium channels, particularly NaV1.7. Certain isotopically-labeled compounds, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e., ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

[0251] Substitution with heavier isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

[0252] Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor

occupancy. Isotopically-labeled compounds can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Testing Compounds

[0253] The assessment of the compounds of the invention in mediating, especially inhibiting, the sodium channel ion flux can be determined using the assays described hereinbelow. Alternatively, the assessment of the compounds in treating conditions and diseases in humans may be established in industry standard animal models for demonstrating the efficacy of compounds in treating pain. Animal models of human neuropathic pain conditions have been developed that result in reproducible sensory deficits (allodynia, hyperalgesia, and spontaneous pain) over a sustained period of time that can be evaluated by sensory testing. By establishing the degree of mechanical, chemical, and temperature induced allodynia and hyperalgesia present, several physiopathological conditions observed in humans can be modeled allowing the evaluation of pharmacotherapies.

[0254] In rat models of peripheral nerve injury, ectopic activity in the injured nerve corresponds to the behavioural signs of pain. In these models, intravenous application of the sodium channel blocker and local anesthetic lidocaine can suppress the ectopic activity and reverse the tactile allodynia at concentrations that do not affect general behaviour and motor function (Mao, J. and Chen, L.L, *Pain* (2000), 87:7-17). Allometric scaling of the doses effective in these rat models, translates into doses similar to those shown to be efficacious in humans (Tanelian, D.L. and Brose, W.G., Anesthesiology (1991), 74(5):949-951). Furthermore, Lidoderm®, lidocaine applied in the form of a dermal patch, is currently an FDA approved treatment for post-herpetic neuralgia (Devers, A. and Glaler, B.S., *Clin. J. Pain* (2000), 16(3):205-8).

[0255] The present invention readily affords many different means for identification of sodium channel modulating agents that are useful as therapeutic agents. Identification of modulators of sodium channel can be assessed using a variety of in vitro and in vivo assays, e.g., measuring current, measuring membrane potential, measuring ion flux, (e.g., sodium or guanidinium), measuring sodium concentration, measuring second messengers and transcription levels, and using e.g., voltage-sensitive dyes, radioactive tracers, and patch-clamp electrophysiology.

[0256] One such protocol involves the screening of chemical agents for ability to modulate the activity of a sodium channel thereby identifying it as a modulating agent.

[0257] A typical assay described in Bean et al., *J. General Physiology* (1983), 83:613-642, and Leuwer, M., et al., *Br. J. Pharmacol.* (2004), 141(1):47-54, uses patch-clamp techniques to study the behaviour of channels. Such techniques are known to those skilled in the art, and may be developed, using current technologies, into low or medium throughput assays for evaluating compounds for their ability to modulate sodium channel behaviour.

[0258] Throughput of test compounds is an important consideration in the choice of screening assay to be used. In some strategies, where hundreds of thousands of compounds are to be tested, it is not desirable to use low throughput means. In other cases, however, low throughput is satisfactory to identify important differences between a limited number of compounds. Often it will be necessary to combine assay types to identify specific sodium channel modulating compounds.

[0259] Electrophysiological assays using patch clamp techniques is accepted as a gold standard for detailed characterization of sodium channel compound interactions, and as described in Bean et al., op. cit. and Leuwer, M., et al., op. cit. There is a manual low-throughput screening (LTS) method which can compare 2-10 compounds per day; a recently developed system for automated medium-throughput screening (MTS) at 20-50 patches (i.e. compounds) per day; and a technology from Molecular Devices Corporation (Sunnyvale, CA) which permits automated high-throughput screening (HTS) at 1000-3000 patches (i.e. compounds) per day.

[0260] One automated patch-clamp system utilizes planar electrode technology to accelerate the rate of drug discovery. Planar electrodes are capable of achieving high-resistance, cells-attached seals followed by stable, low-noise whole-cell recordings that are comparable to conventional recordings. A suitable instrument is the PatchXpress 7000A (Axon Instruments Inc, Union City, CA). A variety of cell lines and culture techniques, which include adherent cells as well as cells growing spontaneously in suspension are ranked for seal success rate and stability. Immortalized cells (e.g. HEK and CHO) stably expressing high levels of the relevant sodium ion channel can be adapted into high-density suspension cultures.

[0261] Other assays can be selected which allow the investigator to identify compounds which block specific states of the channel, such as the open state, closed state or the resting state,

or which block transition from open to closed, closed to resting or resting to open. Those skilled in the art are generally familiar with such assays.

[0262] Binding assays are also available. Designs include traditional radioactive filter based binding assays or the confocal based fluorescent system available from Evotec OAI group of companies (Hamburg, Germany), both of which are HTS.

[0263] Radioactive flux assays can also be used. In this assay, channels are stimulated to open with veratridine or aconitine and held in a stabilized open state with a toxin, and channel blockers are identified by their ability to prevent ion influx. The assay can use radioactive 22[Na] and 14[C] guanidinium ions as tracers. FlashPlate and Cytostar-T plates in living cells avoids separation steps and are suitable for HTS. Scintillation plate technology has also advanced this method to HTS suitability. Because of the functional aspects of the assay, the information content is reasonably good.

[0264] Yet another format measures the redistribution of membrane potential using the FLIPR system membrane potential kit (HTS) available from Molecular Dynamics (a division of Amersham Biosciences, Piscataway, NJ). This method is limited to slow membrane potential changes. Some problems may result from the fluorescent background of compounds. Test compounds may also directly influence the fluidity of the cell membrane and lead to an increase in intracellular dye concentrations. Still, because of the functional aspects of the assay, the information content is reasonably good.

[0265] Sodium dyes can be used to measure the rate or amount of sodium ion influx through a channel. This type of assay provides a very high information content regarding potential channel blockers. The assay is functional and would measure Na+ influx directly. CoroNa Red, SBFI and/or sodium green (Molecular Probes, Inc. Eugene OR) can be used to measure Na influx; all are Na responsive dyes. They can be used in combination with the FLIPR instrument. The use of these dyes in a screen has not been previously described in the literature. Calcium dyes may also have potential in this format.

[0266] In another assay, FRET based voltage sensors are used to measure the ability of a test compound to directly block Na influx. Commercially available HTS systems include the VIPR™ II FRET system (Life Technologies, or Aurora Biosciences Corporation, San Diego, CA, a division of Vertex Pharmaceuticals, Inc.) which may be used in conjunction with FRET dyes, also available from Aurora Biosciences. This assay measures sub-second responses to voltage

changes. There is no requirement for a modifier of channel function. The assay measures depolarization and hyperpolarizations, and provides ratiometric outputs for quantification. A somewhat less expensive MTS version of this assay employs the FLEXstation™ (Molecular Devices Corporation) in conjunction with FRET dyes from Aurora Biosciences. Other methods of testing the compounds disclosed herein are also readily known and available to those skilled in the art.

[0267] Modulating agents so identified are then tested in a variety of in vivo models so as to determine if they alleviate pain, especially chronic pain or other conditions such as cancer and pruritus (itch) with minimal adverse events. The assays described below in the Biological Assays Section are useful in assessing the biological activity of the instant compounds.

[0268] Typically, the efficacy of a compound of the invention is expressed by its IC50 value ("Inhibitory Concentration – 50%"), which is the measure of the amount of compound required to achieve 50% inhibition of the activity of the target sodium channel over a specific time period. For example, representative compounds of the present invention have demonstrated IC50's ranging from less than 100 nanomolar to less than 10 micromolar in the patch voltage clamp NaV1.7 electrophysiology assay described herein.

[0269] In another aspect of the invention, the compounds of the invention can be used in in vitro or in vivo studies as exemplary agents for comparative purposes to find other compounds also useful in treatment of, or protection from, the various diseases disclosed herein.

[0270] Another aspect of the invention relates to inhibiting NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, or NaV1.9 activity, preferably NaV1.7 activity, in a biological sample or a mammal, preferably a human, which method comprises administering to the mammal, preferably a human, or contacting said biological sample with a compound as described herein or a pharmaceutical composition comprising a compound as described herein. The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[0271] Inhibition of NaV1.1, NaV1.2, NaV1.3, NaV1.4, NaV1.5, NaV1.6, NaV1.7, NaV1.8, or NaV1.9 activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, the study of sodium

ion channels in biological and pathological phenomena; and the comparative evaluation of new sodium ion channel inhibitors.

[0272] The compounds of the invention (or stereoisomers, geometric isomers, tautomers, solvates, metabolites, isotopes, pharmaceutically acceptable salts, or prodrugs thereof) and/or the pharmaceutical compositions described herein which comprise a pharmaceutically acceptable excipient and one or more compounds of the invention, can be used in the preparation of a medicament for the treatment of sodium channel-mediated disease or condition in a mammal.

Combination Therapies

[0273] The compounds of the invention may be usefully combined with one or more other compounds of the invention or one or more other therapeutic agent or as any combination thereof, in the treatment of sodium channel-mediated diseases and conditions. For example, a compound of the invention may be administered simultaneously, sequentially or separately in combination with other therapeutic agents, including, but not limited to:

1. opiates analgesics, e.g., morphine, heroin, cocaine, oxymorphine, levorphanol, levallorphan, oxycodone, codeine, dihydrocodeine, propoxyphene, nalmefene, fentanyl, hydrocodone, hydromorphone, meripidine, methadone, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine and pentazocine;
2. non-opiate analgesics, e.g., acetomeniphen, salicylates (e.g., aspirin);
3. nonsteroidal antiinflammatory drugs (NSAIDs), e.g., ibuprofen, naproxen, fenoprofen, ketoprofen, celecoxib, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin and zomepirac;
4. anticonvulsants, e.g., carbamazepine, oxcarbazepine, lamotrigine, valproate, topiramate, gabapentin and pregabalin;
5. antidepressants such as tricyclic antidepressants, e.g., amitriptyline, clomipramine, despramine, imipramine and nortriptyline;
6. COX-2 selective inhibitors, e.g., celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, and lumiracoxib;

7. alpha-adrenergics, e.g., doxazosin, tamsulosin, clonidine, guanfacine, dexmetatomidine, modafinil, and 4-amino-6,7-dimethoxy-2-(5- methane sulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;
8. barbiturate sedatives, e.g., amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobartital, secobarbital, talbutal, theamylal and thiopental;
9. tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g., (αR, 9R)-7-[3,5-bis(trifluoromethyl)benzyl)]-8,9,10,11-tetrahydro-9-methyl- 5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]-naphthyridine-6-13-dione (TAK-637), 5-[[2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethylphenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant or 3-[[2-methoxy5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);
10. coal-tar analgesics, in particular paracetamol;
11. serotonin reuptake inhibitors, e.g., paroxetine, sertraline, norfluoxetine (fluoxetine desmethyl metabolite), metabolite demethylsertraline, '3 fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, cericlamine, trazodone and fluoxetine;
12. noradrenaline (norepinephrine) reuptake inhibitors, e.g., maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, buproprion, buproprion metabolite hydroxybuproprion, nomifensine and viloxazine (Vivalan®)), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (S,S)-reboxetine, and venlafaxine duloxetine neuroleptics sedative/anxiolytics;
13. dual serotonin-noradrenaline reuptake inhibitors, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine, milnacipran and imipramine;
14. acetylcholinesterase inhibitors such as donepezil;
15. 5-HT3 antagonists such as ondansetron;
16. metabotropic glutamate receptor (mGluR) antagonists;
17. local anaesthetic such as mexiletine and lidocaine;
18. corticosteroid such as dexamethasone;
19. antiarrhythimics, e.g., mexiletine and phenytoin;

20. muscarinic antagonists, e.g., tolterodine, propiverine, tropsium chloride, darifenacin, solifenacin, temiverine and ipratropium;
21. cannabinoids;
22. vanilloid receptor agonists (e.g., resinferatoxin) or antagonists (e.g., capsazepine);
23. sedatives, e.g., glutethimide, meprobamate, methaqualone, and dichloralphenazone;
24. anxiolytics such as benzodiazepines,
25. antidepressants such as mirtazapine,
26. topical agents (e.g., lidocaine, capsacin and resiniferotoxin);
27. muscle relaxants such as benzodiazepines, baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol and orphrenadine;
28. anti-histamines or H1 antagonists;
29. NMDA receptor antagonists;
30. 5-HT receptor agonists/antagonists;
31. PDEV inhibitors;
32. Tramadol®;
33. cholinergic (nicotinc) analgesics;
34. alpha-2-delta ligands;
35. prostaglandin E2 subtype antagonists;
36. leukotriene B4 antagonists;
37. 5-lipoxygenase inhibitors; and
38. 5-HT3 antagonists.

[0274] Sodium channel-mediated diseases and conditions that may be treated and/or prevented using such combinations include but not limited to, pain, central and peripherally mediated, acute, chronic, neuropathic as well as other diseases with associated pain and other central nervous disorders such as epilepsy, anxiety, depression and bipolar disease; or cardiovascular disorders such as arrhythmias, atrial fibrillation and ventricular fibrillation; neuromuscular disorders such as restless leg syndrome and muscle paralysis or tetanus; neuroprotection against stroke, neural trauma and multiple sclerosis; and channelopathies such as erythromyalgia and familial rectal pain syndrome.

[0275] As used herein "combination" refers to any mixture or permutation of one or more compounds of the invention and one or more other compounds of the invention or one or more additional therapeutic agent. Unless the context makes clear otherwise, "combination" may include simultaneous or sequentially delivery of a compound of the invention with one or more

therapeutic agents. Unless the context makes clear otherwise, "combination" may include dosage forms of a compound of the invention with another therapeutic agent. Unless the context makes clear otherwise, "combination" may include routes of administration of a compound of the invention with another therapeutic agent. Unless the context makes clear otherwise, "combination" may include formulations of a compound of the invention with another therapeutic agent. Dosage forms, routes of administration and pharmaceutical compositions include, but are not limited to, those described herein.

Computer-aided Molecular Design Methods

[0276] CryoEm structures of NaV1.7 receptors that contain the VSD4 binding site, particularly at better than 3 Angstrom resolution, such as the structure represented in the PDB file (hereinbelow), can be used to carry out computer-based methods of molecular design. The methods herein could also be applied to X-ray crystallographic structures of comparable resolution if obtained.

[0277] Computer-based methods of molecular design typically rely on computer programs available and familiar to those skilled in the art of computational chemistry, computer-aided molecular design, molecular modeling, or rational drug design. Such computer programs are designed to be operated on any or all of a desktop workstation, laptop, or super-computer, and/or may utilize processing resources and storage functions commonly referred to as cloud computing. Such programs may utilize any or all of: molecular mechanics ("force field) representations or quantum mechanical calculations of molecular properties. Such programs may permit the serial docking of tens, hundreds, thousands, tens of thousands, hundreds of thousands, or millions of computer-stored molecular structures into a model of the NaV1.7 binding site such as that provided herewith. It is to be understood that "docking" as used herein means obtaining a preferential fit of a given molecular structure, spatially, into the model, based on some scoring function (based on energetic and/or steric criteria), and permitting multiple conformations of a given molecule to be tested.

[0278] It is further to be understood that computer-aided design of molecules to fit the binding site may include fitting a scaffold into the binding site and permitting a designer to choose and test representative subsitutents on said scaffold for goodness of fit. It is also to be understood that certain computer representations permit the structure of the binding site itself to experience some flexibility such that test inhibitor molecules of varying structure may be tested.

[0279] By fits spatially and preferentially is meant that a molecule possesses a 3-dimensional structure, such as obtainable from one of its conformations, that is accommodated geometrically by a cavity or pocket of a protein, such as on the surface or in a solvent accessible cavity.

[0280] It is further to be understood that it may not be necessary to use an atomic structural model of an entire receptor, such as the NaV1.7 receptor, for the purpose of identifying additional binding compounds. It may be sufficient to dock molecular structures into a model that comprises a portion of the NaV1.7 receptor that encompasses the ligand binding site. As used herein, the term "portion" or "portion thereof" when referring to the NaV1.7 binding site, is intended to mean the atomic coordinates corresponding to a sufficient number of residues or their atoms that interaction with a compound capable of binding to the site can be accurately described. This can include receptor residues having an atom within about 4.5 Angstrom of a bound compound or a moiety thereof. Particularly useful subsets of the coordinates include, but are not limited to, coordinates of single domains of NaV1.7, in particular the ligand binding domain, coordinates of residues lining an active site such as the ligand binding site, coordinates of residues that participate in important intramolecular, or intermolecular, contacts at an interface, and Cα coordinates. For example, the coordinates of one domain of a protein that contains the active site may be used to design inhibitors that bind to that site, even though the protein is fully described by a larger set of atomic coordinates. Therefore, a set of atomic coordinates that define the entire polypeptide chain of NaV1.7, or the NaV1.7 ligand binding receptor, although useful for many applications, do not necessarily need to be used for the methods described herein.

[0281] Structure coordinates for the NaV1.7 receptor or portions thereof according to Appendix 1 may be modified by mathematical manipulation. Such manipulations include, but are not limited to, fractionalization of the raw structure coordinates, additions to, or subtractions from, sets of the raw structure coordinates, by a constant amount inversion, rotation, or reflection the raw structure coordinates, and any combination of the foregoing. Appendix 1 contains coordinates of the VSD4 domain that does not include the channel portion of the receptor.

[0282] Those having skill in the art will recognize that atomic structure coordinates are not without error. Thus, it is to be understood that, preferably, any set of structure coordinates obtained for NaV1.7 that have a root mean square deviation ("r.m.s.d.") of from about 0.5 to about 0.7 Ångstrom, or from 0.5 to 0.7 Ångstrom, when superimposed, using backbone atoms (N, Cα, C and O), on the structure whose coordinates are found in Appendix 1, are considered to be identical with the structure coordinates listed herein when at least about 50% to 100% of the

backbone atoms of NaV1.7 are included in the superposition. Less preferably, a set of structure coordinates obtained for NaV1.7 that have a r.m.s.d. of from about 0.7 to about 1.0 Ångstrom, or from 0.7 to 1.0 Ångstrom, when superimposed, can be considered to be identical with the structure coordinates listed herein.

[0283] Computer-stored molecular structures, or atomic structural information, as used herein, is taken to mean coordinates and identities of atoms found in a molecule or complex, presented or stored in any one of the formats referred to hereinbelow. From atomic structural information it is typically possible to deduce further information important to a chemist, such as the location and type of chemical bonds between atoms in the molecule or complex. It is further to be understood that atomic structural information may be incomplete in the sense that one or more atoms, particularly hydrogen atoms, is missing. However, where there are such missing atoms, it is further to be understood that one of ordinary skill in the art is usually able to deduce the likely position and identity of such atoms, particularly using one or more software programs that would be readily available. The term "atomic model", or "atomic structural model" may also find use herein. Such terms refer to a set of identities and coordinates for the atoms in a molecule presented in such a way that a 3-dimensional representation of the molecule may be presented to one of skill in the art on, for example, a computer display. Such a 3-dimensional representation may be further manipulated by, for example, rotating or translating it on the display, or by altering its conformation so that the 3-dimensional disposition of its constituent atoms is changed, even though the way in which they are bonded to one another remains unchanged.

[0284] All format representations of the atomic structure coordinates described herein may be used according to methods herein. Accordingly, the present invention encompasses the structure coordinates and other information, *e.g.*, amino acid sequence, connectivity tables, vector-based representations, temperature factors, etc., used to generate the three-dimensional structure of the NaV1.7 receptor and its binding site for use in the software programs described herein and other software programs.

[0285] While Cartesian coordinates are important and convenient representations of the three-dimensional structure of a protein or polypeptide, those of ordinary skill in the art will readily recognize that other representations of the structure are also useful. Therefore, the three-dimensional structure of a protein, receptor, small organic molecule, or polypeptide, as discussed herein, includes not only the Cartesian coordinate representation, but also all alternative representations of the three-dimensional distribution of atoms. For example, atomic coordinates

may be represented as a Z-matrix, wherein a first atom of the molecule is chosen, a second atom is placed at a defined distance from the first atom, a third atom is placed at a defined distance from the second atom so that the first, second and third atoms, when taken in order, make a defined angle. Each subsequent atom is placed at a defined distance from a previously placed atom to make a specified angle with respect to a third atom, and at a specified torsion angle with respect to a fourth atom.

[0286] Atomic coordinates may also be represented as a Patterson function, wherein all interatomic vectors are drawn and are then placed with their tails at the origin. This representation is particularly useful for locating heavy atoms in a unit cell. In addition, atomic coordinates may be represented as a series of vectors having magnitude and direction and drawn from a chosen origin to each atom in the molecule structure. Furthermore, the positions of atoms in a 3-dimensional structure may be represented as fractions of the unit cell (fractional coordinates), or in spherical polar coordinates.

[0287] Additional information, such as thermal parameters, which measure the motion of each atom in a crystal structure, chain identifiers, which identify the particular chain of a multi-chain protein in which an atom is located, and connectivity information, which indicates to which atoms a particular atom is bonded, are also useful for representing a 3-dimensional molecular structure.

[0288] A variety of data processor programs and formats can be used to store the sequence and structure information on a computer readable medium. Such formats include, but are not limited to, Protein Data Bank ("PDB") format (Research Collaboratory for Structural Bioinformatics; pdb101.rcsb.org/learn/guide-to-understanding-pdb-data); Structure-data ("SD") file format (MDL Information Systems, Inc.; Dalby et al., J. Chem. Inf. Comp. Sci. 32:244-255, (1992)), and line-notation, e.g., as used in SMILES (Weininger, D., "SMILES, a Chemical Language and Information System. 1. Introduction to Methodology and Encoding Rules," J. Chem. Inf. Comp. Sci., 28:31-36, (1988)), and CHUCKLES (Siani, M. A., Weininger, D., Blaney, J., "CHUCKLES: a method for representing and searching peptide and peptoid sequences on both monomer and atomic levels," *J. Chem. Inf. Comp. Sci.*, 34:588-593, (1994)).

[0289] Methods of converting between various formats read by different computer software will be readily apparent to those of ordinary skill in the art, and programs for carrying out such conversions are widely available, either as stand-alone programs, e.g., BABEL (Walters, P. and Stahl, M., © 1992 – 1996), available as open-source, or integrated into other software packages.

[0290] Ultimately, molecules to be tested for goodness of fit to the NaV1.7 binding site ("test molecules") have to be quantified for goodness of fit, and preferably selected for testing by means of biochemical assay. Testing may also include synthesizing prior to assaying, in the case of compounds that are not commercially available.

[0291] After the 3-dimensional structure of a NaV1.7 receptor, with or without a bound ligand, is determined, the structural information, comprising atomic coordinates, can be stored electronically. Accordingly, the present invention encompasses machine readable media embedded with the three-dimensional structure of the model described herein, or with portions thereof and/or other physicochemical data. By providing a computer readable medium having stored thereon the atomic coordinates of the invention, one of skill in the art can routinely access the atomic coordinates of the invention, or portions thereof, and related information for use in modeling and design programs, as described in detail hereinbelow.

[0292] As used herein, "machine readable medium" or "computer readable medium" refers to any media that can be read and accessed directly by a computer or scanner. Such media include, but are not limited to: magnetic storage media, such as floppy discs, hard discs and magnetic tape; optical storage media such as optical discs; CD-ROM, CD-R or CD-RW, and DVD; electronic storage media such as RAM or ROM; and hybrids of these categories such as magnetic/optical storage media. In a preferred embodiment, the information is provided in the form of a machine-readable data storage medium such as a CD-Rom, or on a computer hard-drive. Such media further include paper on which is recorded a representation of the atomic structure coordinates, e.g., Cartesian coordinates, that can be read by a scanning device and converted into a three-dimensional structure with optical character recognition (OCR) technology. The choice of the data storage structure will generally be based on the means chosen to access the stored information.

[0293] The machine readable data storage medium can also be used in computational methods of interactive ligand design, specifically the design of synthetic molecules that bind to the NaV1.7 receptor. In one embodiment of the present invention, the structure coordinates of the ligand binding site of NaV1.7 are useful for identifying and/or designing compounds that bind NaV1.7 so that new therapeutic agents may ultimately be developed.

[0294] Methods of rational drug design and virtual screening that utilize the coordinates of the proteins of the present invention are preferably performed on one or more computers that comprise at least one central-processing unit for processing machine readable data, coupled via a bus to working memory, a user interface, a network interface, and a machine-readable memory.

In preferred embodiments, one or more such computing systems distributed over a computer network are utilized.

[0295] In such computing systems: machine-readable memory comprises a data storage material encoded with machine-readable data, wherein the data comprises the structural coordinates of at least one receptor of NaV1.7, with or without a ligand bound thereto; working memory stores an operating system, optionally one or more molecular structure databases, optionally one or more pharmacophores derived from structural coordinates, a graphical user interface and instructions for processing machine-readable data comprising one or more molecular modelling programs such as a deformation energy calculator, a homology modelling tool, a de novo design tool, a "docking tool", a database search engine, a 2D-3D structure converter and a file format interconverter.

[0296] A suitable computer system may be any of the varieties of laptop or desktop personal computer, or workstation, or a networked or mainframe computer or super-computer, that would be available to one of ordinary skill in the art. For example, a suitable computer system may be a personal computer, a workstation, or may be a supercomputer of the type formerly popular in academic computing environments. Computer system may also support multiple processors, in particular GPU processors.

[0297] A suitable operating system may be any variety that runs on any of the foregoing computer systems. For example, in one embodiment, operating system 112 is selected from the UNIX family of operating systems. It may also be a LINUX operating system. In another embodiment, operating system 112 is a Windows operating system such as Windows10. In yet another embodiment, operating system 112 is a Macintosh operating system such as MacOS X and later variants, from Apple, Inc.

[0298] A graphical user interface ("GUI") is preferably used for displaying representations of structural coordinates or variations thereof, in 3-dimensional form on user a interface. The GUI also preferably permits the user to manipulate the display of the structure that corresponds to structural coordinates of a NaV1.7 receptor in a number of ways, including, but not limited to: rotations in any of three orthogonal degrees of freedom; translations; projecting the structure on to a 2-dimensional representation; zooming in on specific portions of the structure; coloring of the structure according to a property that varies amongst to different regions of the structure; displaying subsets of the atoms in the structure; coloring the structure by atom type; displaying tertiary structure such as .alpha.-helices and .beta.-sheets as solid or shaded objects; and

displaying a surface of a small molecule, peptide, or protein, as might correspond to, for example, a solvent accessible surface, also optionally colored according to some property. Structural coordinates are also optionally copied into computer system memory to facilitate manipulations with one or more of the molecular modelling programs.

[0299] A network interface may optionally be used to access one or more molecular structure databases stored in the memory of one or more other computers.

[0300] The computational methods of the present invention may be carried out with commercially available programs which run on, or with computer programs that are developed specially for the purpose and implemented on, any of the foregoing computer systems. Commercially available programs typically comprise large integrated molecular modelling packages that contain multiple types of functionality, and are available from vendors such as OpenEye Scientific Software, Inc. (Santa Fe, NM), Chemical Computing Group (Montreal, Canada), and Schrödinger, Inc. (New York, NY).

[0301] Alternatively, the computational methods of the present invention may be performed with one or more stand-alone programs each of which carries out one of the functions performed by integrated molecular modelling progams. In particular, certain aspects of the display and visualization of molecular structures may be accomplished by specialized tools).

[0302] In still another embodiment, the structure of the NaV1.7 ligand binding site can be used to computationally screen small molecule databases for compounds that can bind in whole, or in part, to NaV1.7. In this screening, the quality of fit of such entities or compounds to the binding site may be judged by methods such as shape complementarity or by estimated interaction energy, according to anumber of different methods known to those skilled in the art.

[0303] Compounds fitting the NaV1.7 binding site serve as a starting point for an iterative design, synthesis and test cycle in which new compounds are selected and optimized for desired properties including affinity, efficacy, and selectivity with respect to the NaV1.7 binding site and various mutated forms thereof. For example, the compounds can be subjected to additional modification, such as replacement and/or addition of substituents of a core structure identified for a particular class of binding compounds, modeling and/or activity screening if desired, and then subjected to additional rounds of testing.

[0304] By "modeling" is meant quantitative and qualitative analysis of molecular structure and/or function based on atomic structural information and interaction models of a receptor and a

ligand agonist or antagonist. Modeling thus includes conventional numeric-based molecular dynamic and energy minimization models, interactive computer graphic models, modified molecular mechanics models, distance geometry and other structure-based constraint models. Modeling is preferably performed using a computer and may be further optimized using methods familiar to one of ordinary skill in the art.

[0305] Identification of a not previously understood binding conformation to the NaV1.7 binding site has made it possible to apply the principles of molecular modeling to design more compounds that are complementary to the structure of the binding site. Accordingly, computer programs that employ various docking algorithms can be used to identify compounds that fit into the ligand binding domain of NaV1.7. Fragment-based docking can also be used to build molecules inside the NaV1.7 binding site, by placing molecular fragments that have a complementary fit with the site, thereby optimizing intermolecular interactions. Techniques of computational chemistry can also be used to optimize the geometry of the bound conformations.

[0306] Docking may be accomplished using commercially available software such as reviewed in: Pagadala NS, Syed K, Tuszynski J. "Software for molecular docking: a review", *Biophys Rev.*, 2017, 9(2):91-102. Docking is typically followed by energy minimization and molecular dynamics simulations of the docked molecule, using molecular mechanics forcefields. See for example, those reviewed in: Cole, D. J., et al., "The future of force fields in computer-aided drug design", *Future Med. Chem.*, 11(18), (2019).

[0307] Once a compound has been designed or selected by methods such as those described hereinabove, the efficiency with which that compound may bind to the binding site of NaV1.7 may be tested and optimized by computational evaluation. For example, a compound that has been designed or selected to function as an inhibitor (antagonist) of NaV1.7 preferably occupies a volume that does not overlap with the volume occupied by the active site residues. An effective inhibitor of NaV1.7 activity preferably demonstrates a relatively small difference in energy between its bound and free states (i.e., it has a small deformation energy of binding). Thus, the most efficient inhibitors of NaV1.7 should preferably be designed with a deformation energy of binding of not greater than about 10 kcal/mol or, even more preferably, not greater than about 7 kcal/mol. Molecules that bind to NaV1.7 may interact with the receptor in more than one conformation that is similar in overall binding energy. In such cases, the deformation energy of binding is preferably taken to be the difference between the energy of the free compound and the average energy of the conformations observed when the inhibitor binds to the receptor.

[0308] A compound selected or designed for binding to NaV1.7 may be further computationally optimized so that in its bound state it would lack repulsive electrostatic interactions with the NaV1.7 structure. Such repulsive electrostatic interactions include non-complementary interactions such as repulsive charge-charge, dipole-dipole and charge-dipole interactions. Specifically, the sum of all electrostatic interactions between the inhibitor and the receptor when the inhibitor is bound to it preferably make a neutral or favorable contribution to the enthalpy of binding.

[0309] Specific computer software is available in the art to evaluate compound deformation energy and electrostatic interaction. Examples of programs designed for such uses fall into approximately three levels of sophistication. The crudest level of approximation, molecular mechanics, is also the cheapest to compute and can most usefully be used to calculate deformation energies. Molecular mechanics programs find application for calculations on small organic molecules as well as polypeptides, nucleic acids, proteins, and most other biomolecules.

[0310] An intermediate level of sophistication comprises the so-called "semi-empirical" methods, which are relatively inexpensive to compute and are most frequently employed for calculating deformation energies of organic molecules. Examples of program packages that provide semi-empirical capability are reviewed in: Christensen, A. S., et al., *Chem. Rev.*, 2016, 116, 9, 5301–5337.

[0311] The highest level of sophistication is achieved by those programs that employ so-called ab initio quantum chemical methods and methods of density functional theory, for example those reviewed in: Kulik, et al., *J. Phys. Chem. B*, 2012, 116, 41, 12501–12509. These programs may be installed, for instance, on a computer workstation, as is well-known in the art. Other hardware systems and software packages will be known to those skilled in the art.

[0312] In general, databases of small molecules can be computationally screened to identify molecules that are likely to bind in whole, or in part, to a NaV1.7 binding site of interest. In such screening, the quality of fit of molecules to the binding site may be judged by any of a number of methods that are familiar to one of ordinary skill in the art, including shape complementarity or by estimated interaction energy Such methods are preferably applicable to ranking compounds for their ability to binding to the NaV1.7 receptor.

[0313] In a preferred method, potential binding compounds may be obtained by rapid computational screening. Such a screening comprises testing a large number, which may be

hundreds, or may preferably be thousands, or more preferably tens of thousands, or even more preferably hundreds of thousands of molecules whose formulae are known and for which at least one conformation can be readily computed.

[0314] The databases of small molecules include any virtual or physical database, such as electronic and physical compound library databases. Preferably, the molecules are obtained from one or more molecular structure databases that are available in electronic form and any proprietary database of compounds with known medicinal properties, as is found in a large or small pharmaceutical company.

[0315] The molecules in such databases for use with the present invention are preferably stored as a connection table, with or without a 2D representation that comprises coordinates in just 2 dimensions, say x and y, for facilitating visualization on a computer display. The molecules are more preferably stored as at least one set of 3D coordinates corresponding to an experimentally derived or computer-generated molecular conformation. If the molecules are only stored as a connection table or a 2D set of coordinates, then it can be necessary to generate a 3D structure for each molecule before proceeding with a computational screen, for example, if the molecules are to be docked into a receptor structure during screening. Programs for converting 2D molecular structures or molecule connection tables to 3D structures are available to those skilled in the art.

[0316] As part of a computational screen, it is possible to "dock" 3D structures of molecules from a database into the NaV1.7 binding site on a high throughput basis. Such a procedure can normally be subject to a number of user-defined parameters and thresholds according to desired speed of throughput and accuracy of result. Such parameters include the number of different starting positions from which to start a docking simulation and the number of energy calculations to carry out before rejecting or accepting a docked structure. Such parameters and their choices are familiar to one of ordinary skill in the art. Structures from the database can be selected for synthesis to test their ability to bind NaV1.7 if their docked energy is below a certain threshold. Methods of docking are further described elsewhere herein.

[0317] Alternatively, it is possible to carry out a "molecular similarity" search for molecules that are potential inhibitors of NaV1.7. If a pharmacophore has been developed from a knowledge of the NaV1.7 binding site, then molecules whose structures map on to that pharmacophore are to be found. A pharmacophore defines a set of contact sites on the surface of the binding site, accompanied by the distances between them. A similarity search attempts to find

molecules in a database that have at least one favorable 3D conformation whose structure overlaps favorably with the pharmacophore. For example, a pharmacophore may comprise a lipophilic pocket at a particular position, a hydrogen-bond acceptor site at another position and a hydrogen bond donor site at yet another specified position accompanied by distance ranges between them. A molecule that could potentially fit into the active site is one that can adopt a conformation in which a H-bond donor in the active site can reach the H-bond acceptor site on the pharmacophore, a H-bond acceptor in the active site can simultaneously reach the H-bond donor site of the pharmacophore and, for example, a group such as a phenyl ring can orient itself into the lipophilic pocket.

[0318] Even where a pharmacophore has not been developed, molecular similarity principles may be employed in a database searching regime (see, for example, Johnson, M. A.; Maggiora, G. M., Eds. Concepts and Applications of Molecular Similarity, New York: John Wiley & Sons (1990)) if at least one molecule that fits well into the NaV1.7 binding site is known. In a preferred embodiment, it is possible to search for molecules that have certain properties in common with those of the molecule(s) known to bind. For example, such properties include numbers of hydrogen bond donors or numbers of hydrogen bond acceptors, or overall hydrophobicity within a particular range of values. Alternatively, even where a pharmacophore is not known, similar molecules may be selected on the basis of optimizing an overlap criterion with the molecule of interest. For example, where the structures of test molecules that bind are known, a model of the test molecule may be superimposed over the model of the NaV1.7 structure.

[0319] In searching a molecular structure database, a specialized database searching tool that permits searching molecular structures and sub-structures is typically employed, as is familiar to one of skill in the art.

[0320] Molecules that bind to the NaV1.7 binding site can be designed by a number of methods, including: exploiting available structural and functional information; by deriving a quantitative structure-activity relationship (QSAR); and by using a combination of such information to design new compound libraries. In particular, focused libraries having molecular diversity at one or more particular groups attached to a core structure or scaffold, may be used. Preferably, structural data is incorporated into the iterative design process. For example, one of skill in the art may use one of several methods to screen molecules or fragments for their ability to associate with the NaV1.7 binding site. This process may begin with visual inspection of, for example, the NaV1.7 binding site on a computer screen. Selected fragments or chemical entities

may then be positioned into the site, or a portion thereof. Docking may be accomplished using computer software as described hereinabove, followed by energy minimization and molecular dynamics with standard molecular mechanics force-fields, as also described hereinabove.

[0321] The design of molecules that bind to NaV1.7 generally involves consideration of two factors. The molecule must be capable of first physically, and second structurally, associating with NaV1.7. The physical interactions underpinning this association can be covalent or non-covalent. For example, covalent interactions may be important for designing irreversible or "suicide" inhibitors of a protein. Non-covalent molecular interactions that are important in the association of NaV1.7 with molecules that bind to it include hydrogen bonding, ionic, van der Waals, and hydrophobic interactions. Structurally, the compound must be able to assume a conformation that allows it to associate with the binding site of NaV1.7. Although certain portions of the compound will not necessarily directly participate in this association with NaV1.7, those portions may still influence the overall conformation of the molecule. This, in turn, may have a significant impact on potency. Such conformational requirements include the overall three-dimensional structure and orientation of a functional group or moleculein relation to all or a portion of the binding site, or the spacing between functional groups of a compound comprising several functional groups that directly interact with NaV1.7.

[0322] In general, the potential binding effect of a compound on NaV1.7 may be analyzed prior to its actual synthesis and testing by the use of computer modeling techniques. If the theoretical structure of the given compound suggests insufficient interaction and association between it and the NaV1.7 binding site, synthesis and testing of the compound need not be carried out. However, if computer modeling indicates a strong interaction, the molecule may then be synthesized and tested for its ability to bind to the NaV1.7 binding site and thereby inhibit its activity. In this manner, costly synthesis of ineffective compounds may be avoided.

[0323] Among the computational techniques that enable the rational design of molecules that bind to NaV1.7, it is key to have access to visualization tools, programs for calculating properties of molecules, and programs for fitting ligand structures into three-dimensional representations of the receptor binding site. Computer program packages for facilitating each of these capabilities have been referred to herein, and are available to one of ordinary skill in the art. Visualization of molecular properties, such as field properties that vary through space, can also be particularly important and may be aided by computer programs familiar to those of skill in the art.

[0324] A molecular property of particular interest when assessing suitability of drug compounds is its hydrophobicity. An accepted and widespread measure of hydrophobicity is LogP, the $\log_{10}$ of the octanol-water partition coefficient. It is customary to use the value of LogP for a designed molecule to assess whether the molecule could be suitable for transport across a cell membrane, if it were to be administered as a drug. Measured values of LogP are available for many compounds. Methods and programs for calculating LogP are also available, and are particularly useful for molecules that have not been synthesized or for which no experimental value of LogP is available.

[0325] Once an NaV1.7-binding compound has been optimally selected or designed, as described hereinabove, substitutions may then be made in some of its atoms or chemical groups in order to improve or modify its binding properties. Generally, initial substitutions are conservative, *i.e.*, the replacement group will have approximately the same size, shape, hydrophobicity, polarity and charge as the original group. For selection of appropriate groups, any of several chemical models can be used, e.g., isolobal or isosteric analogies. Groups known to be bio-isosteres of one another are particularly preferred. One of skill in the art will understand that substitutions known in the art to alter conformation are preferably avoided. Such altered chemical compounds may then be analyzed for efficiency of binding to NaV1.7 by the same computer methods described hereinabove.

[0326] Suitable test compounds can be designed, as is further described herein, or can be obtained from a library of compounds, and include, by means of illustration and not limitation, small organic molecules, peptides and peptidomimetics. A library of compounds may be a combinatorial library, generated either in the laboratory, or virtually in a computer, or may be a computer-encoded library of molecules that are commercially available from one or more vendors. The library of compounds may further be a commercially available selection of molecules that has been selected for a particular property, or for representative diversity of properties.

[0327] In some embodiments, the atomic coordinates of a compound that fits into the NaV1.7 binding site also can be used for modeling to identify compounds or fragments that bind the site. Thus, the present invention also provides for a computational method that uses three dimensional models of a NaV1.7 receptor, such as derived from CryoEM, preferably containing coordinates of a bound molecule. Such models can be said to be experimentally derived, as opposed to derived computationally, such as by homology modeling. Generally, the computational method of

designing a NaV1.7 receptor ligand involves determining which amino acid or amino acid residues of the NaV1.7 receptor binding site interact with at least one moiety ("first moiety") of the ligand, by using a three dimensional model that comprises the NaV1.7 receptor binding site. The method further comprises selecting at least one chemical modification of the first moiety to produce a second moiety that either decreases or increases an interaction between the interacting amino acid residue and the second moiety when compared to the interaction between the interacting amino acid residue and the original moiety. Such a modification can be carried out virtually, by using a computer modeling program as further described herein, or in the laboratory, as applied to a sample of the molecule or by synthesizing an analog that differs from the initial molecule by such a modification.

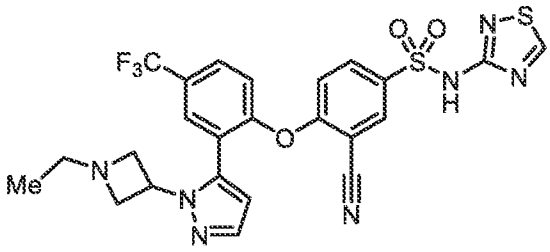
[0328] Computational methods may further comprise quantifying a change in interaction between the interacting amino acid in the NaV1.7 binding site and the ligand after modification of the first moiety. The modification can either enhance or reduce a hydrogen bonding interaction, a charge interaction, a hydrophobic interaction, a van der Waals interaction, or a dipole interaction between the second moiety and the interacting amino acid, as compared to the interaction between the first moiety and the interacting amino acid. Chemical modifications will often enhance or reduce interactions between an atom of a NaV1.7 binding site amino acid and an atom of a ligand.

NaV1.7 Binding Modes

[0329] Voltage-gated sodium channels have been shown to have four (4) discrete voltage sensing domains (VSD). VSD4 has been identified as the most promising target for molecular design, and comprises 4 helices, S1 – S4.

[0330] Inhibitors of the NaV1.7 VSD4 binding domain have been identified previously as falling within two chemical classes: aryl-sulfonamides (such as GNE-616, *J. Med. Chem.*, 62, 4091 (2019), and acyl sulfonamides (such as GDC-0276, *J. Med. Chem.*, 64, 2953 (2021)).

[0331] Hitherto, only one small molecule co-crystal structure of an inhibitor (GX-936) bound to the NaV1.7 VSD4 domain has been published (*Science*, (2015), 350 (6267), aac5464). In this structure, one key interaction is between an anionic "warhead" on the ligand and two arginine residues in the receptor binding site, and a second is an aryl/CF_3 interaction between phCF_3 on the ligand and a pi-stacking relationship with residue Y1537 in the binding pocket.



GX-936

[0332] Conversely, efforts to determine co-crystal structures of acyl sulfonamide ligands bound to NaV1.7 have been unsuccessful, meaning that attempts at molecular design has been in some sense, "blind", and relying on structure-activity relationships (SAR) and assumptions as to the respective binding modes of both series. As shown in FIG. 1, the two classes of compounds exhibited "pseudoparallel" SAR trends while apparently demonstrating competitive binding. Proposals to reconcile the different SAR while rationalizing their binding poses were unsatisfactory (see, *e.g.*, *J. Med. Chem.* 62, 908 (2019)). FIGs. 2A and 2B show schematics of proposed binding poses of aryl- and acyl-sulfonamide compounds of the prior art.

[0333] By using cryo-EM, however, as described elsewhere herein, it was possible to independently confirm the binding posture of the aryl-sulfonamide series of compounds while, for the first time revealing that the acyl-sulfonamide compounds bind to the VSD4 domain in a different manner,with accompanying changes in protein conformation.

[0334] Specifically, it becomes clear that aryl sulfonamides bind between helices S2 and S3, pushing residue Tyr1537 "upwards"; the helices S3/S4 form a "wall" abutting the anionic "warhead". Conversely, acyl sulfonamides bind to a different pocket of the VSD4 domain, wherein the binding site is between helices S3 and S4, the Tyr1537 residue is pointed "down" into intrahelical space between S2 and S3.

[0335] This is summarized in FIGs. 3A, 3B. Other facets of the differentiated binding poses between the two classes of compounds are as follows: Aryl sulfonamides interact with receptor residues R1602 and R1608; Acyl sulfonamides interact with receptor residuces R1605 and R1608. Furthermore, in the bound aryl sulfonamide configurations, S3/S4 pocket interactions appear to be largely lipophlic space filling. Conversely, for bound acyl sulfonamides, the ligands' "tail" reside wholly in the plasma membrane that surrounds the receptor.

[0336] The understanding of two distinct binding poses leads to the possibility that molecules could be designed that simultaneously bind both pockets, thereby relying less on membrane

interactions for potency, and more for an increased interaction with a larger and more complex binding pocket. The principle behind devising such "hybrid" molecules is illustrated in FIG. 4.

[0337] Various aspects of design and properties of "hybrid" molecules that bind NaV1.7 are shown in FIGs. 4, 5A – 5C, 6A – 6C, 7A – 7E, 8A and 8B. Such features can be utilized to rationalize the binding properties of molecules exemplified herein as well as to design further molecules consistent with the instant invention.

[0338] The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention.

EXAMPLES

[0339] The following examples serve to provide guidance to a skilled artisan to prepare and use the compounds, compositions and methods of the invention. While a particular embodiment of the present invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the inventions. Furthermore, while the Examples are not presented in a continuous sequence, the numbers are unique. Gaps in the numbering sequence are not indicative of omitted material (either intentionally or unintentionally), and the assignment of a particular number to a particular compound or example is arbitrary and without significance.

[0340] The chemical reactions in the examples described can be readily adapted to prepare a number of other compounds of the invention, and alternative methods for preparing the compounds of this invention are deemed to be within the scope of this invention. For example, the synthesis of non-exemplified compounds according to the invention can be successfully performed by modifications apparent to those skilled in the art, for example, by appropriately protecting interfering groups by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions.

[0341] In the examples below, unless otherwise indicated all temperatures are set forth in degrees Celsius. Commercially available reagents were purchased from suppliers such as Aldrich Chemical Company, Lancaster, TCI or Maybridge and were used without further purification unless otherwise indicated. The reactions set forth below were done under a positive pressure of nitrogen or argon or with a drying tube (unless otherwise stated) in anhydrous solvents, and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried. ^{1}H NMR spectra were

obtained in deuterated $CDCl_3$, d_6-DMSO, CH_3OD or d_6-acetone solvent solutions (reported in ppm) using or trimethylsilane (TMS) or residual non-deuterated solvent peaks as the reference standard. When peak multiplicities are reported, the following abbreviates are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hz (Hertz).

[0342] Although the preparation of the free-base or a specific salt form may be illustrated in the Examples herein, it is understood that the free-base and its acid or base salt forms can be interconverted using standard techniques

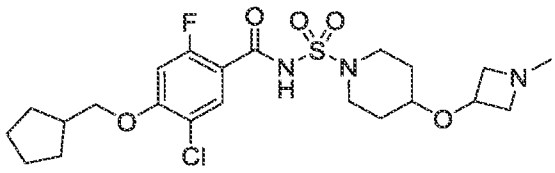
[0343] All abbreviations used to describe reagents, reaction conditions or equipment are intended to be consistent with the definitions set forth in the "List of standard abbreviates and acronyms". The chemical names of discrete compounds of the invention were obtained using the structure naming feature of ChemDraw naming program. Structures in the Examples herein are shown with a formula ((I), (II), etc., as described elsewhere herein) that each respective compound falls within.

Abbreviations

MeCN	Acetonitrile
EtOAc	Ethyl acetate
DCM	Dichloromethane
DIPEA	Diisopropylethylamine
DEA	Diethylamine
DMAP	4-dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
FA	Formic acid
IPA	Isopropyl alcohol
TFA	Trifluoroacetic acid
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
HCl	Hydrochloric acid
HPLC	High Pressure Liquid Chromatography
LCMS	Liquid Chromatography Mass Spectrometry
MeOH	Methanol
NMP	N-methyl-2-pyrrolidone

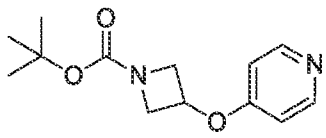
RT	Retention time
SFC	Supercritical Fluid Chromatography
THF	Tetrahydrofuran
TEA	Triethylamine

Example 1: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide



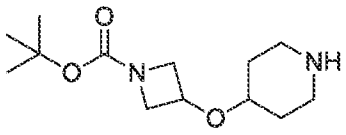
(I)

Step 1: *tert*-butyl 3-(pyridin-4-yloxy)azetidine-1-carboxylate



[0344] To a solution of 4-hydroxypyridine (6.2 g, 65.19 mmol) in THF (190 ml) was added PPh_3 (21.37 g, 81.49 mmol), 1-boc-3-hydroxyazetidine (14.12 g, 81.49 mmol) and DIAD (16.16 ml, 81.49 mmol) at room temperature. The mixture was stirred at 70 °C for 16 h. After cooling to room temperature, the reaction was concentrated in vacuo. The reaction mixture was dissolved in 1.0 M aqueous HCl solution (100 mL) and extracted with DCM (100 mL). The aqueous lawyer was adjusted to pH = 12 using 1.0 M aqueous NaOH and then extracted with DCM (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to afford the title compound (6.11 g, 75%) as colorless oil. LCMS (ESI) m/z: 251.1 $[M+H]^+$.

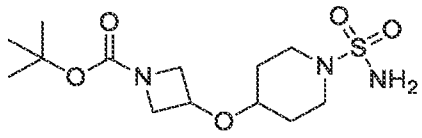
Step 2: *tert*-butyl 3-(piperidin-4-yloxy)azetidine-1-carboxylate



[0345] To a solution of PtO_2 (5.47 g, 24.09 mmol) in EtOH (150 mL) was added *tert*-butyl 3-(pyridin-4-yloxy)azetidine-1-carboxylate (6.7 g, 26.77 mmol) and TsOH (5.07 g, 29.45 mmol). The mixture was stirred at 45 °C for 48 h under hydrogen atmosphere (45 psi). After cooling to room temperature, the mixture was added 1 M NaOH aqueous solution (200 mL) and stirred for 10 min, then the mixture was filtered, concentrated in vacuo to remove most EtOH and extracted

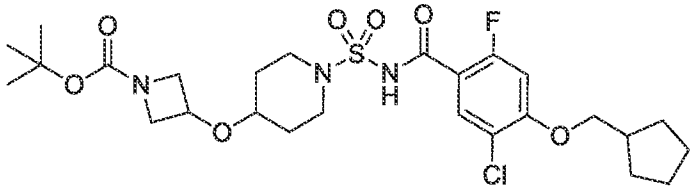
with DCM (100 mL x 4). The combined organic layers were washed with brine (100 mL x 2), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (solvent gradient: 0 - 10% MeOH in DCM (1% $NH_3 \cdot H_2O$)) to afford the title compound (2.5 g, 36%) as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.36 - 4.28 (m, 1H), 4.12 - 4.04 (m, 2H), 3.86 - 3.77 (m, 2H), 3.47 - 3.41 (m, 1H), 3.18 - 3.12 (m, 2H), 2.82 - 2.71 (m, 2H), 1.99 - 1.88 (m, 2H), 1.65 - 1.52 (m, 2H), 1.44 (s, 9H).

Step 3: *tert*-butyl 3-((1-sulfamoylpiperidin-4-yl)oxy)azetidine-1-carboxylate



[0346] To a mixture of *tert*-butyl 3-(piperidin-4-yloxy)azetidine-1-carboxylate (500 mg, 1.95 mmol) in 1,4-dioxane (20 mL) was added sulfamide (469 mg, 4.88 mmol). The resulting mixture was stirred at 110 °C for 16 h under nitrogen atmosphere. After cooling to room temperature, the reaction was added water (20 mL), extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (600 mg, crude) as a yellow solid that required no further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 4.35 - 4.27 (m, 1H), 4.15 - 4.10 (m, 2H), 3.86 - 3.79 (m, 2H), 3.55 - 3.45 (m, 1H), 3.45 - 3.30 (m, 2H), 3.15 - 3.00 (m, 2H), 1.94 - 1.83 (m, 2H), 1.79 - 1.68 (m, 2H), 1.44 (s, 9H).

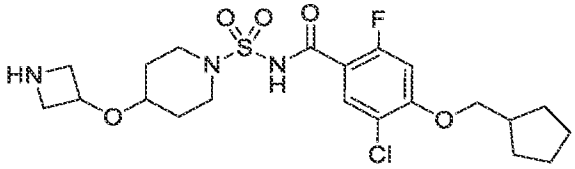
Step 4: *tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)azetidine-1-carboxylate



[0347] To a mixture of DMAP (0.63 g, 5.13 mmol) and EDCI (0.59 g, 3.08 mmol) in DCM (35 mL) was added 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-benzoic acid (0.7 g, 2.57 mmol) and *tert*-butyl 3-[(1-sulfamoyl-4-piperidyl)oxy]azetidine-1-carboxylate (0.86 g, 2.57 mmol). The resulting mixture was stirred at room temperature for 16 h under nitrogen atmosphere. The reaction was quenched with 10% citric aqueous solution (50 mL) and extracted with DCM (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel

chromatography (solvent gradient: 0 - 7% MeOH in DCM) to afford the title compound (1.2 g, 79%) as a white solid. LCMS (ESI) m/z: 490.2 $[M-100+H]^+$.

Step 5: *N*-((4-(azetidin-3-yloxy)piperidin-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide

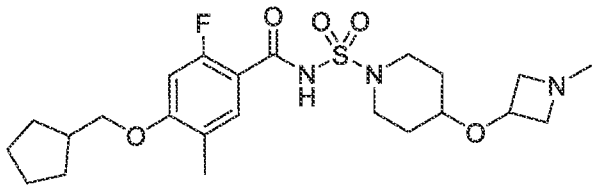


[0348] To a solution of 2,2,2-trifluoroacetic acid (1.3 mL, 17.31 mmol) in DCM (17 mL) was added *tert*-butyl 3-[[1-[[5-chloro-4-(cyclopentylmethoxy)-2-fluoro-benzoyl]sulfamoyl]-4-piperidyl]oxy]azetidine-1-carboxylate (1.2 g, 2.03 mmol) at room temperature. The mixture was stirred at room temperature for 1 h. The mixture was concentrated in vacuo, then the residue was dissolved in DCM (30 mL), washed with 10% NaOH aqueous solution (10 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (0.90 g, crude) as a white solid that required no further purification. LCMS (ESI) m/z: 490.1 $[M+H]^+$.

Step 6: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide

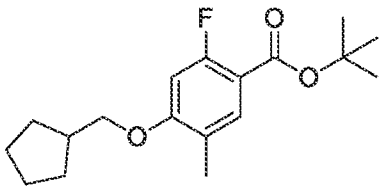
[0349] To a mixture of *N*-((4-(azetidin-3-yloxy)piperidin-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide (200 mg, 0.41 mmol) in DCM (6 mL) was added formaldehyde (0.82 mL, 10.85 mmol, 37% in water) and $NaBH(OAc)_3$ (432 mg, 2.04 mmol). The resulting mixture was stirred at room temperature for 16 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) to pH > 7 and then extracted with DCM (30 mL x 2). The combined organic layers were washed with brine (25 mL), then dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by reverse phase chromatography (solvent gradient: acetonitrile 30 - 60% / (0.2% HCOOH) in water) to afford the title compound (15.48 mg, 7%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.71 (d, J = 7.6 Hz, 1H), 6.96 (d, J = 12.4 Hz, 1H), 4.43 - 4.36 (m, 1H), 4.25 - 4.17 (m, 2H), 3.95 (d, J = 6.8 Hz, 2H), 3.75 - 3.85 (m, 2H), 3.45 - 3.41 (m, 3H), 2.77 (s, 3H), 2.75 - 2.71 (m, 2H), 2.32 - 2.25 (m, 1H), 1.83 - 1.72 (m, 4H), 1.64 - 1.50 (m, 4H), 1.45 - 1.32 (m, 4H). LCMS (ESI) m/z: 504.2 $[M+H]^+$.

Example 2: 4-(cyclopentylmethoxy)-2-fluoro-5-methyl-*N*-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide



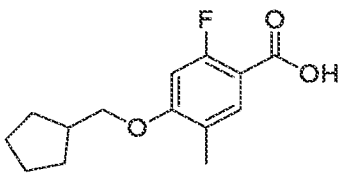
I

Step 1: *tert*-butyl 4-(cyclopentylmethoxy)-2-fluoro-5-methylbenzoate



[0350] A mixture of *tert*-butyl 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-benzoate (500 mg, 1.52 mmol), methylboronicacid (0.27 g, 4.56 mmol) and K_3PO_4 (0.97 g, 4.56 mmol) in toluene (7 mL) and water (1 mL) was added $Pd(OAc)_2$ (34 mg, 0.15 mmol) and dicyclohexyl-(2',6'-dimethoxybiphenyl-2-yl)-phosphane (62 mg, 0.15 mmol). The mixture was stirred at 100 °C under nitrogen atmosphere for 3 h. After cooling to room temperature, the reaction was diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to afford the title compound (370 mg, 78%) as a yellow soild. LCMS (ESI) m/z: 253.1 $[M-56+H]^+$.

Step 2: 4-(cyclopentylmethoxy)-2-fluoro-5-methylbenzoic acid



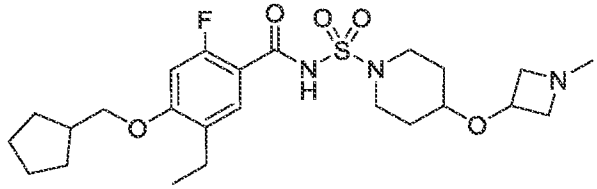
[0351] To a solution of 2,2,2-trifluoroacetic acid (3.0 mL, 40.39 mmol) in DCM (6 mL) was added *tert*-butyl 4-(cyclopentylmethoxy)-2-fluoro-5-methyl-benzoate (370 mg, 1.2 mmol) at room temperature. The mixture was stirred at room temperature for 1 h. The mixture was concentrated in vacuo. The residue was added *n*-heptane (5 mL) and stirred at room temperature for 0.5 h. The resultant mixture was filtered to afford the title compound (130 mg, 42%) as a white solid that required no further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, J = 8.4 Hz, 1H), 6.58

(d, *J* = 12.4 Hz, 1H), 3.89 (d, *J* = 6.8 Hz, 2H), 2.46 - 2.38 (m, 1H), 2.20 (s, 3H), 1.91 - 1.84 (m, 2H), 1.70 - 1.61 (m, 4H), 1.44 - 1.37 (m, 2H).

Step 3: 4-(cyclopentylmethoxy)-2-fluoro-5-methyl-*N*-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide

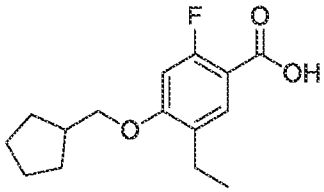
[0352] Following the procedure described in Example **1** and making non-critical variations as required to replace 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-benzoic acid with 4-(cyclopentylmethoxy)-2-fluoro-5-methylbenzoic acid, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, *J* = 8.8 Hz, 1H), 6.73 (d, *J* = 12.4 Hz, 1H), 4.40 - 4.30 (m, 1H), 4.15 - 4.04 (m, 2H), 3.87 (d, *J* = 6.8 Hz, 2H), 3.63 - 3.61 (m, 2H), 3.47 - 3.35 (m, 3H), 2.85 - 2.75 (m, 2H), 2.67 (s, 3H), 2.35 - 2.24 (m, 1H), 2.09 (s, 3H), 1.86 - 1.71 (m, 4H), 1.68 - 1.48 (m, 4H), 1.47 - 1.29 (m, 4H). LCMS (ESI) m/z: 484.1 $[M+H]^+$.

Example 3: 4-(cyclopentylmethoxy)-5-ethyl-2-fluoro-N-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl) sulfonyl) benzamide



(I)

a. Step 1: 4-(cyclopentylmethoxy)-5-ethyl-2-fluorobenzoic acid



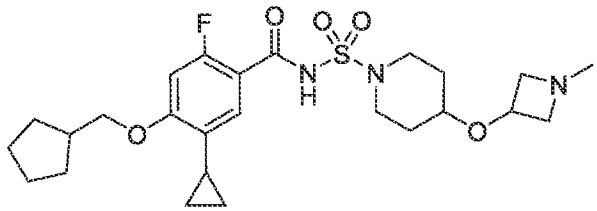
[0353] Following the procedure described in Example **2** and making non-critical variations as required to replace methylboronic acid with ethylboronic acid, the title compound was obtained as a white solid. LCMS (ESI) m/z: 266.9 $[M+H]^+$

Step 2: 4-(cyclopentylmethoxy)-5-ethyl-2-fluoro-N-((4-((1-methylazetidin-3-yl) oxy) piperidin-1-yl) sulfonyl) benzamide

[0354] Following the procedure described in Example **1** and making non-critical variations as required to replace 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid with 4-(cyclopentylmethoxy)-5-ethyl-2-fluorobenzoic acid, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 12.8 Hz, 1H), 4.42 - 4.34 (m, 1H), 4.30 - 4.13 (m, 2H), 3.90 (d, *J* = 6.4 Hz, 2H), 3.78 - 3.69 (m, 2H), 3.53 - 3.42 (m,

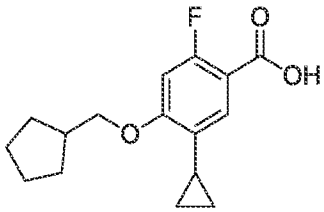
3H), 2.98 - 2.89 (m, 2H), 2.73 (s, 3H), 2.52 - 2.47 (m, 2H), 2.46 - 2.42 (m, 1H), 1.88 - 1.73 (m, 4H), 1.66 - 1.53 (m, 4H), 1.50 - 1.42 (m, 2H), 1.40 - 1.30 (m, 2H), 1.12 (t, J = 7.6 Hz, 3H). LCMS (ESI) m/z: 498.1 $[M+H]^+$.

Example 4: 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluoro-N-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl) sulfonyl) benzamide



(I)

Step 1: 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid

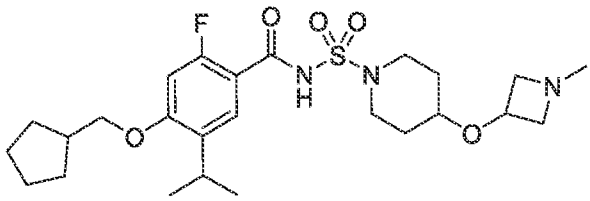


[0355] Following the procedure described in Example **2** and making non-critical variations as required to replace methylboronic acid with cyclopropylboronic acid, the title compound was obtained as a white solid. LCMS (ESI) m/z: 279.2 $[M+H]^+$.

Step 2: 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluoro-N-((4-((1-methylazetidin-3-yl) oxy) piperidin-1-yl) sulfonyl) benzamide

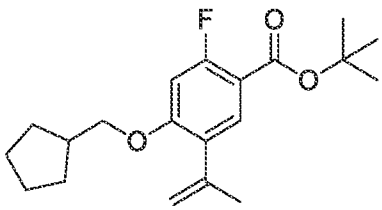
[0356] Following the procedure described in Example **1** and making non-critical variations as required to replace 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid with 4-(cyclopentyl-methoxy)-5-cyclopropyl-2-fluorobenzoic acid, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.15 (d, J = 8.8 Hz, 1H), 6.74 (d, J = 12.8 Hz, 1H), 4.38 - 4.27 (m, 1H), 4.10 - 4.03 (m, 2H), 3.90 (d, J = 6.8 Hz, 2H), 3.62 - 3.50 (m, 2H), 3.45 - 3.35 (m, 3H), 2.90 - 2.78 (m, 2H), 2.65 (s, 3H), 2.37 - 2.28 (m, 1H), 2.03 - 1.95 (m, 1H), 1.85 - 1.73 (m, 4H), 1.64 - 1.51 (m, 4H), 1.46 - 1.29 (m, 4H), 0.90 - 0.84 (m, 2H), 0.61 - 0.54 (m, 2H). LCMS (ESI) m/z: 510.3 $[M+H]^+$.

Example 5: 4-(cyclopentylmethoxy)-2-fluoro-5-isopropyl-*N*-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide



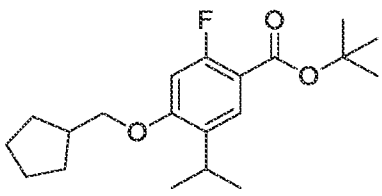
(I)

Step 1: *tert*-butyl 4-(cyclopentylmethoxy)-2-fluoro-5-(prop-1-en-2-yl)benzoate



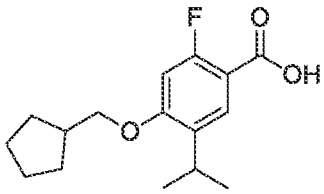
[0357] To a solution of *tert*-butyl 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoate (200 mg, 0.61 mmol), Cs_2CO_3 (595 mg, 1.82 mmol) and 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (123 mg, 0.73 mmol) in 1,4-dioxane (3 mL) and water (0.3 mL) was added XPhos Pd G2 (47 mg, 0.06 mmol) and XPhos (29 mg, 0.06 mmol) under nitrogen atmosphere. The reaction was stirred at 100 °C for 16 h. After cooling to room temperature, the reaction was diluted with water (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine, anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified on silica gel chromatography (solvent gradient: 100% petroleum ether) to afford the title compound (150 mg, 74%) as light yellow oil. LCMS (ESI) m/z: 279.2 $[M-56+H]^+$.

Step 2: *tert*-butyl 4-(cyclopentylmethoxy)-2-fluoro-5-isopropyl-benzoate



[0358] To a solution of *tert*-butyl 4-(cyclopentylmethoxy)-2-fluoro-5-(prop-1-en-2-yl)benzoate (150 mg, 0.45 mmol) in EtOAc (5 mL) was added 10% Pd/C (71 mg, 0.07 mmol). The reaction was stirred under hydrogen atmosphere (15 psi) at room temperature for 16 h. The mixture was filtered and concentrated in vacuo to afford the title compound (150 mg, crude) as colorless oil that required no further purification. LCMS (ESI) m/z: 281.2 $[M-56+H]^+$.

Step 3: 4-(cyclopentylmethoxy)-2-fluoro-5-isopropylbenzoic acid

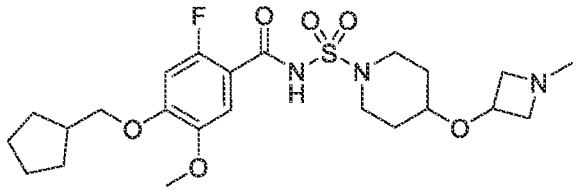


[0359] To a solution of *tert*-butyl 4-(cyclopentylmethoxy)-2-fluoro-5-isopropyl-benzoate (150 mg, 0.45 mmol) in DCM (2 mL) was added 2,2,2-trifluoroacetic acid (1 mL). The reaction was stirred at room temperature for 4 h. The mixture was concentrated in vacuo. The residue was added *n*-heptane (5 mL) and stirred at room temperature for 0.5 h. The resultant mixture was filtered to afford the title compound (120 mg, crude) as a light blue solid that required no further purification. LCMS (ESI) m/z: 281.1 $[M+H]^+$.

Step 4: 4-(cyclopentylmethoxy)-2-fluoro-5-isopropyl-*N*-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide

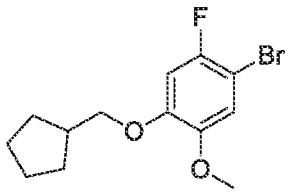
[0360] Following the procedure described in Example **1** and making non-critical variations as required to replace 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid with 4-(cyclopentyl-methoxy)-2-fluoro-5-isopropylbenzoic acid, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, J = 8.8 Hz, 1H), 6.69 (d, J = 12.8 Hz, 1H), 4.30 - 4.27 (m, 1H), 4.05 - 3.96 (m, 2H), 3.87 (d, J = 6.4 Hz, 2H), 3.50 - 3.41 (m, 4H), 3.18 - 3.11 (m, 1H), 2.83 - 2.78 (m, 2H), 2.58 (s, 3H), 2.36 - 2.28 (m, 2H), 1.80 - 1.77 (m, 4H), 1.64 - 1.52 (m, 4H), 1.44 - 1.33 (m, 4H), 1.16 (d, J = 7.2 Hz, 6H). LCMS (ESI) m/z: 512.3 $[M+H]^+$.

Example 6: 4-(cyclopentylmethoxy)-2-fluoro-5-methoxy-*N*-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl) sulfonyl) benzamide



(I)

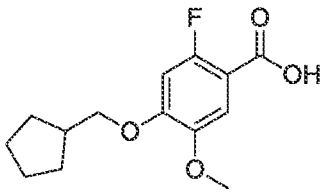
Step 1: 1-bromo-4-(cyclopentylmethoxy)-2-fluoro-5-methoxybenzene



[0361] A solution of K_2CO_3 (1.13 g, 8.14 mmol), NaI (0.61 g, 4.07 mmol), (bromomethyl)cyclopentane (2.0 g, 12.2 mmol) and 4-bromo-5-fluoro-2-methoxyphenol (0.90 g, 4.07 mmol) in DMSO (10 mL) was stirred at 80 °C for 16 h. After cooling to room temperature,

the reaction was diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (30 mL x 4), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to afford the title compound (0.60 g, 86%) as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 6.4 Hz, 1H), 6.70 (d, J = 10.0 Hz, 1H), 3.85 - 3.82 (m, 5H), 2.49 - 2.46 (m, 1H), 1.90 - 1.82 (m, 2H), 1.68 - 1.58 (m, 4H), 1.38 - 1.32 (m, 2H).

Step 2: 4-(cyclopentylmethoxy)-2-fluoro-5-methoxybenzoic acid

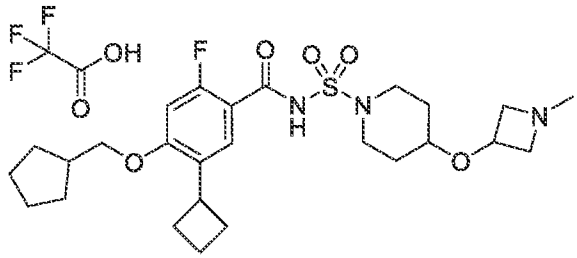


[0362] To a solution of 1-bromo-4-(cyclopentylmethoxy)-2-fluoro-5-methoxy-benzene (0.30 g, 0.99 mmol) in THF (6 mL) was added *n*-BuLi (0.47 mL, 1.19 mmol, 2.5 M) at -78 °C. The mixture was stirred at -78 °C for 1 h. Then CO_2 gas (15 psi) was bubbled. The reaction was stirred at roon temperature for 1 h. The reaction was quenched with water (2 mL), then adjusted to pH < 7 with aqueous HCl (1 M), extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to afford the title compound (80 mg, 30%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 4.0 Hz, 1H), 6.61 (d, J = 12.4 Hz, 1H), 3.89 (d, J = 7.2 Hz, 2H), 3.86 (s, 3H), 2.51 - 2.40 (m, 1H), 1.93 - 1.82 (m, 2H), 1.67 - 1.59 (m, 4H), 1.38 - 1.31 (m, 2H).

Step 3: 4-(cyclopentylmethoxy)-2-fluoro-5-methoxy-*N*-((4-((1-methylazetidin-3-yl)oxy) piperidin-1-yl) sulfonyl) benzamide

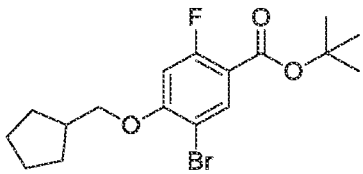
[0363] Following the procedure described in Example **1** and making non-critical variations as required to replace 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid with 4-(cyclopentyl-methoxy)-2-fluoro-5-methoxybenzoic acid, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23 (d, J = 7.2 Hz, 1H), 6.78 (d, J = 12.0 Hz, 1H), 4.39 - 4.28 (m, 1H), 4.11 - 4.03 (m, 2H), 3.85 (d, J = 7.2 Hz, 2H), 3.74 (s, 3H), 3.62 - 3.57 (m, 1H), 3.44 - 3.42 (m, 2H), 2.81 (t, J = 10.0 Hz, 2H), 2.66 (s, 3H), 2.34 - 2.26 (m, 1H), 1.85 - 1.70 (m, 4H), 1.64 - 1.50 (m, 4H), 1.49 - 1.40 (m, 2H), 1.36 - 1.27 (m, 2H). LCMS (ESI) m/z: 500.3 $[M+H]^+$.

Example 7: 5-cyclobutyl-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide 2,2,2-trifluoroacetate



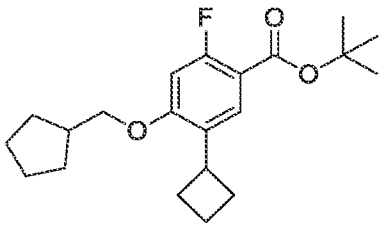
(I)

Step 1: *tert*-butyl 5-bromo-4-(cyclopentylmethoxy)-2-fluorobenzoate



[0364] To a mixture of cyclopentanemethanol (1.4 g, 13.98 mmol) and *tert*-butyl 5-bromo-2,4-difluoro-benzoate (4.51 g, 15.38 mmol) in DMSO (12 mL) was added Cs_2CO_3 (4.55 g, 13.98 mmol) and the reaction mixture was heated at 80 °C for 16 h. After cooling to room temperature, the mixture was diluted with EtOAc (100 mL), washed with brine (100 mL x 5). The organic lawyer was dried over Na_2SO_4, filtered, concentrated in vacuo. The residue was purified by reverse phase chromatography (acetonitrile 65 - 99% / (0.225% HCOOH) in water) to afford the title compound (1.75 g, 33%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.6 Hz, 1H), 6.60 (d, J = 12.4 Hz, 1H), 3.92 (d, J = 6.8 Hz, 2H), 2.37 - 2.49 (m, 1H), 1.92 - 1.83 (m, 2H), 1.74 - 1.60 (m, 4H), 1.58 (s, 9H), 1.45 - 1.37 (m, 2H). LCMS (ESI) m/z: 316.8 $[M-56+H]^+$.

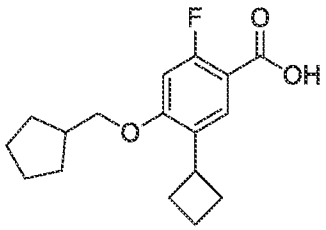
Step 2: *tert*-butyl 5-cyclobutyl-4-(cyclopentylmethoxy)-2-fluorobenzoate



[0365] To a solution of *tert*-butyl 5-bromo-4-(cyclopentylmethoxy)-2-fluorobenzoate (300 mg, 0.8 mmol) in THF (4 mL) was added $Pd(dppf)Cl_2$ (117 mg, 0.16 mmol) and bromo(cyclobutyl)zinc (8.0 mL, 4.02 mmol) under nitrogen atmosphere. The reaction was stirred at 65 °C for 16 h. After cooling to 0 °C, the reaction was quenched with water (10 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was

purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to afford the title compound (140 mg, 50%) as yellow oil. LCMS (ESI) m/z: 293.1 $[M-56+H]^+$.

Step 3: 5-cyclobutyl-4-(cyclopentylmethoxy)-2-fluorobenzoic acid

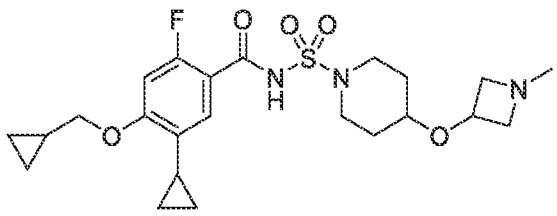


[0366] To a solution of *tert*-butyl 5-cyclobutyl-4-(cyclopentylmethoxy)-2-fluorobenzoate (180 mg, 0.52 mmol) in DCM (5 mL) was added 2,2,2-trifluoroacetic acid (0.38 mL, 5.17 mmol). The reaction was stirred at room temperature for 1 h. The mixture was concentrated in vacuo, treated with *n*-heptane (5 mL) and stirred at room temperature for 0.5 h. The resultant mixture was filtered and the filtrate dried in vacuo to afford the title compound (140 mg, crude) as yellow oil that required no further purification. LCMS (ESI) m/z: 293.2 $[M+H]^+$.

Step 4: 5-cyclobutyl-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide 2,2,2-trifluoroacetate

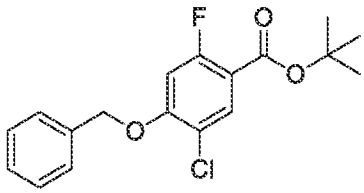
[0367] Following the procedure described in Example **1** and making non-critical variations as required to replace 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid with 5-cyclobutyl-4-(cyclopentylmethoxy)-2-fluorobenzoic acid, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 12.8 Hz, 1H), 4.50 - 4.35 (m, 2H), 4.12 - 4.00 (m, 2H), 3.90 (d, J = 6.8 Hz, 2H), 3.89 - 3.80 (m, 1H), 3.63 - 3.50 (m, 4H), 3.45 - 3.41 (m, 2H), 3.39 - 3.35 (m, 2H), 3.15 - 3.05 (m, 2H), 2.83 (s, 3H), 2.37 - 2.29 (m, 1H), 2.28 - 2.20 (m, 2H), 2.11 - 1.96 (m, 3H), 1.90 - 1.83 (m, 2H), 1.81 - 1.76 (m, 2H), 1.64 - 1.54 (m, 6H), 1.38 - 1.28 (m, 2H), 1.25 - 1.22 (m, 1H). LCMS (ESI) m/z: 524.1 $[M+H]^+$.

Example 9: 5-cyclopropyl-4-(cyclopropylmethoxy)-2-fluoro-*N*-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide



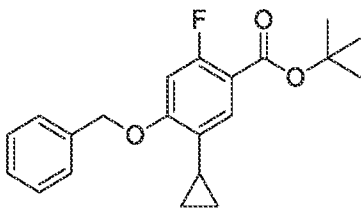
(I)

Step 1: *tert*-butyl 4-(benzyloxy)-5-chloro-2-fluorobenzoate



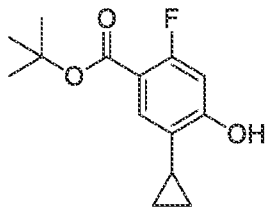
[0368] To a solution of *tert*-butyl 5-chloro-2,4-difluoro-benzoate (5.0 g, 20.11 mmol) and Cs_2CO_3 (13.1 g, 40.22 mmol) in DMSO (50 mL), benzyl alcohol (2.17 g, 20.11 mmol) was added. The reaction was stirred at 80 °C under nitrogen atmosphere for 16 h. After cooling to room temperature, the reaction was diluted with water (100 mL) and extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine (100 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 1% EtOAc in petroleum ether) to afford the title compound (4.7 g, 69%) as colorless oil. LCMS (ESI) m/z: 281.1 $[M-56+H]^+$.

Step 2: *tert*-butyl 4-(benzyloxy)-5-cyclopropyl-2-fluorobenzoate



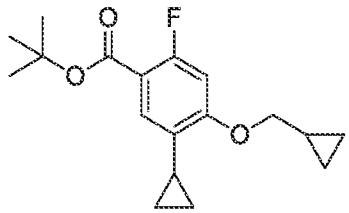
[0369] To a solution of *tert*-butyl 4-benzyloxy-5-chloro-2-fluoro-benzoate (2.5 g, 7.42 mmol), K_3PO_4 (4.73 g, 22.27 mmol) and cyclopropylboronicacid (956 mg, 11.13 mmol) in toluene (17.5 mL) and water (2.5 mL), $Pd(OAc)_2$ (166 mg, 0.74 mmol) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (304 mg, 0.74 mmol) was added under nitrogen atmosphere at room temperature. The reaction was stirred at 100 °C for 16 h. After cooling to room temperature, the reaction was diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 2% EtOAc in petroleum ether) to afford the title compound (2.1 g, 82%) as colorless oil. LCMS (ESI) m/z: 287.1 $[M-56+H]^+$.

Step 3: *tert*-butyl 5-cyclopropyl-2-fluoro-4-hydroxybenzoate



[0370] To a solution of *tert*-butyl 4-(benzyloxy)-5-cyclopropyl-2-fluorobenzoate (1.4 g, 4.09 mmol) in ethanol (30 mL) and Pd/C (870 mg, 0.82 mmol) was added at room temperature. The mixture was stirred at room temperature under hydrogen atmosphere (15 psi) for 16 h. The reaction was filtered and concentrated in vacuo to afford the title compound (1.0 g, crude) as colorless oil that required no further purification. LCMS (ESI) m/z: 197.1 $[M-56+H]^+$.

Step 4: *tert*-butyl 5-cyclopropyl-4-(cyclopropylmethoxy)-2-fluorobenzoate

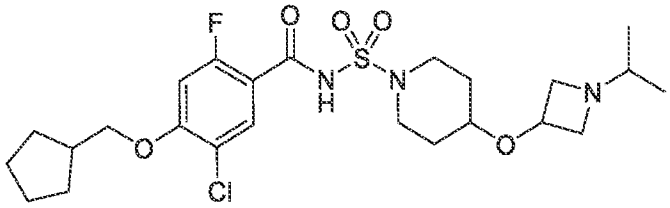


[0371] To a stirred solution of *tert*-butyl 5-cyclopropyl-2-fluoro-4-hydroxy-benzoate (0.25 g, 0.99 mmol) in DMF (2.5 mL) was added TBAI (0.04 g, 0.10 mmol), K_2CO_3 (0.55 g, 3.96 mmol) and cyclopropylmethyl bromide (0.67 g, 4.95 mmol) at room temperature under nitrogen atmosphere. Then reaction was stirred at 70 °C for 16 h. After cooling to room temperature, the reaction was diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (30 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (300 mg, 92%) as yellow oil that required no further purification. LCMS (ESI) m/z: 251.2 $[M-56+H]^+$.

Step 5: 5-cyclopropyl-4-(cyclopropylmethoxy)-2-fluoro-*N*-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl) sulfonyl)benzamide

[0372] Following the procedure described in Example **1** and making non-critical variations as required to replace 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid with 5-cyclopropyl-4-(cyclopropylmethoxy)-2-fluorobenzoic acid, the title compound was obtained as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.14 (d, J = 8.8 Hz, 1H), 6.67 (d, J = 12.8 Hz, 1H), 4.35 - 4.23 (m, 1H), 4.05 - 3.94 (m, 2H), 3.87 (d, J = 6.8 Hz, 2H), 3.55 - 3.45 (m, 5H), 2.85 - 2.70 (m, 2H), 2.59 (s, 3H), 2.10 - 1.95 (m, 1H), 1.85 - 1.70 (m, 2H), 1.50 - 1.35 (m, 2H), 1.30 - 1.15 (m, 1H), 0.93 - 0.80 (m, 2H), 0.63 - 0.52 (m, 4H), 0.39 - 0.31 (m, 2H). LCMS (ESI) m/z: 482.1 $[M+H]^+$.

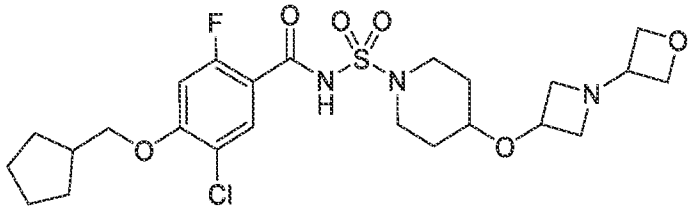
Example 10: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((1-isopropylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide



(I)

[0373] To a mixture of acetone (1.5 mL, 20.35 mmol) in acetonitrile (5 mL) was added *N*-[[4-(azetidin-3-yloxy)-1-piperidyl]sulfonyl]-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-benzamide (50 mg, 0.10 mmol) and $NaBH(OAc)_3$ (32 mg, 0.15 mmol). The resulting mixture was stirred at room temperature for 16 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) to pH > 7, extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by reverse phase chromatography (acetonitrile 30-60% / (0.2% HCOOH) in water) to afford the title compound (11 mg, 21%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (d, J = 7.6 Hz, 1H), 7.13 (d, J = 11.2 Hz, 1H), 4.34 - 4.40 (m, 1H), 4.25 - 4.30 (m, 2H), 4.00 (d, J = 6.8 Hz, 2H), 3.85 - 3.95 (m, 2H), 3.46 - 3.32 (m, 4H), 2.87- 2.96 (m, 2H), 2.37 - 2.33 (m, 1H), 1.89 - 1.73 (m, 4H), 1.63 - 1.47 (m, 6H), 1.38 - 1.32 (m, 2H), 1.10 (d, J = 6.4 Hz, 6H). LCMS (ESI) m/z: 532.1 $[M+H]^+$.

Example 11: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((1-(oxetan-3-yl)azetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide

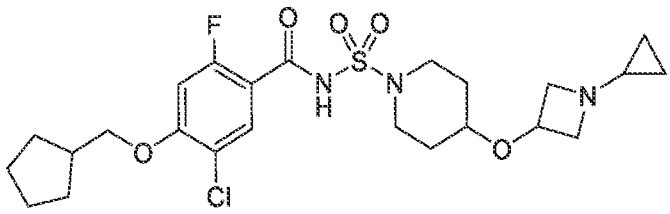


(I)

[0374] To a mixture of 3-oxetanone (29 mg, 0.41 mmol) in DCM (10 mL) was added *N*-[[4-(azetidin-3-yloxy)-1-piperidyl]sulfonyl]-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-benzamide (100 mg, 0.20 mmol) and $NaBH(OAc)_3$ (86 mg, 0.41 mmol). The resulting mixture was stirred at room temperature for 16 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) to pH > 7 and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by reverse phase chromatography (acetonitrile 30 - 60% / (0.05% $NH_3 \cdot H_2O$ + 10mM NH_4HCO_3) in water) to afford the title compound (11 mg, 9%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (d, J = 7.6 Hz, 1H), 6.96 (d, J = 12.4 Hz, 1H), 4.76 - 4.72 (m, 2H),

4.50 - 4.45 (m, 2H), 4.37 - 4.30 (m, 1H), 3.99 (d, *J* = 6.8 Hz, 2H), 3.91 - 3.85 (m, 1H), 3.78 - 3.73 (m, 2H), 3.64 - 3.59 (m, 2H), 3.57 - 3.52 (m, 1H), 3.24 - 3.18 (m, 4H), 2.46 - 2.39 (m, 1H), 1.92 - 1.85 (m, 4H), 1.72 - 1.61 (m, 6H), 1.49 - 1.42 (m, 2H). LCMS (ESI) m/z: 546.3 $[M+H]^+$.

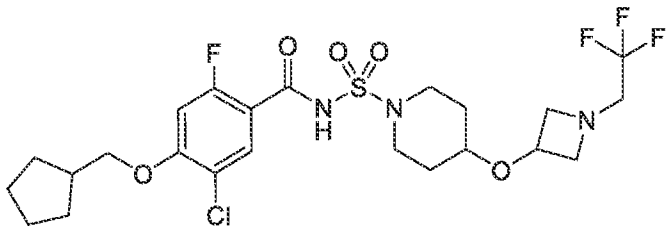
Example 12: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-((1-cyclopropylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)-2-fluorobenzamide



(I)

[0375] To a mixture of *N*-[[4-(azetidin-3-yloxy)-1-piperidyl]sulfonyl]-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-benzamide (100 mg, 0.20 mmol) in EtOH (3 mL) was added (1-ethoxycyclopropoxy)trimethylsilane (213 mg, 1.22 mmol), acetic acid (0.01 ml, 0.20 mmol), $NaBH_3CN$ (77 mg, 1.22 mmol), and 4 Å molecular sieve (100 mg). The resulting mixture was stirred at 50 °C for 1 h. After cooling to room temperature, the mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) (pH > 7), diluted with water (10 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by reverse phase chromatography (acetonitrile 27 - 57% / (0.2% HCOOH) in water) to afford the title compound. ^1H NMR (400 MHz, DMSO-d_6) δ 7.71 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 12.4 Hz, 1H), 4.25 - 4.15 (m, 1H), 3.99 (d, *J* = 6.8 Hz, 2H), 3.75 - 3.83 (m, 2H), 3.50 - 3.40 (m, 5H), 3.00 - 2.85 (m, 2H), 2.40 - 2.20 (m, 2H), 1.91 - 1.69 (m, 4H), 1.67 - 1.50 (m, 4H), 1.48 - 1.26 (m, 4H), 0.58 - 0.27 (m, 4H). LCMS (ESI) m/z: 530.3 $[M+H]^+$.

Example 13: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((1-(2,2,2-trifluoroethyl)azetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide

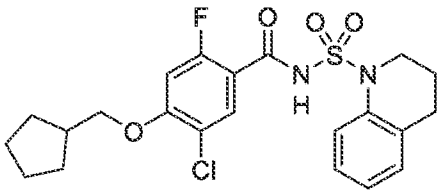


(I)

[0376] To a mixture of *N*-[[4-(azetidin-3-yloxy)-1-piperidyl]sulfonyl]-5-chloro-4-(cyclopentyl-methoxy)-2-fluoro-benzamide (80 mg, 0.16 mmol) in MeCN (2 mL) was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (47 mg, 0.20 mmol) and NEt_3 (20 mg, 0.20 mmol). The resulting mixture was stirred at room temperature for 16 h. The reaction was diluted with

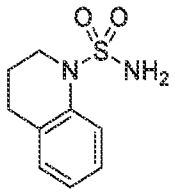
water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by reverse phase chromatography (acetonitrile 65 - 95% / (0.2% HCOOH) in water) to afford the title compound (5 mg, 5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 12.0 Hz, 1H), 4.25 - 4.15 (m, 1H), 4.03 (d, J = 6.8 Hz, 2H), 3.65 - 3.72 (m, 2H), 3.56 - 3.41 (m, 4H), 3.30 - 3.15 (m, 2H), 3.15 - 3.00 (m, 3H), 2.40 - 2.27 (m, 1H), 1.87 - 1.70 (m, 4H), 1.69 - 1.52 (m, 4H), 1.50 - 1.40 (m, 2H), 1.39 - 1.31 (m, 2H). LCMS (ESI) m/z: 572.2 $[M+H]^+$.

Example 14: 5-chloro-4-(cyclopentylmethoxy)-*N*-((3,4-dihydroquinolin-1(2*H*)-yl)sulfonyl)-2-fluorobenzamide



(I)

Step 1: 3,4-dihydroquinoline-1(2*H*)-sulfonamide



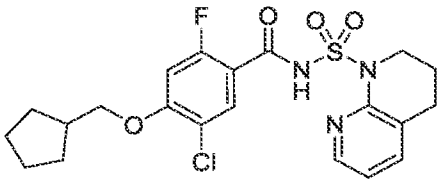
[0377] To a stirred solution of 1,2,3,4-tetrahydroquinoline (500 mg, 3.75 mmol) in 1-methyl-2-pyrrolidinone (22 mL) was added sulfamoylchloride (867 mg, 7.51 mmol) at 0 °C. The mixture was stirred at room temperature under nitrogen atmosphere for 16 h. The reaction was diluted with water (50 mL) and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (50 mL x 4), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (550 mg, crude) as a yellow solid that required no further purification. LCMS (ESI) m/z: 213.2 $[M+H]^+$.

Step 2: 5-chloro-4-(cyclopentylmethoxy)-*N*-((3,4-dihydroquinolin-1(2*H*)-yl)sulfonyl)-2-fluorobenzamide

[0378] To a mixture of 3,4-dihydroquinoline-1(2*H*)-sulfonamide (195 mg, 0.92 mmol) and DMAP (224 mg, 1.83 mmol) in DCM (15 mL) was added 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-benzoic acid (250 mg, 0.92 mmol) and EDCI (210 mg, 1.1 mmol). The resulting mixture was stirred at room temperature for 16 h under nitrogen atmosphere. The reaction was quenched with 10% citric aqueous solution (30 mL) and extracted with DCM (30 mL x 3). The combined

organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by reverse phase chromatography (acetonitrile 70 - 100% / (0.2% HCOOH) in water) to afford the title compound (53 mg, 12%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (s, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.24 - 7.10 (m, 3H), 7.05 - 6.97 (m, 1H), 4.00 (d, J = 6.8 Hz, 2H), 3.90 (t, J = 6.0 Hz, 2H), 2.73 (t, J = 6.4 Hz, 2H), 2.38 - 2.25 (m, 1H), 2.00 - 1.90 (m, 2H), 1.82 - 1.70 (m, 2H), 1.68 - 1.47 (m, 4H), 1.40 - 1.27 (m, 2H). LCMS (ESI) m/z: 489.0 $[M+Na]^+$.

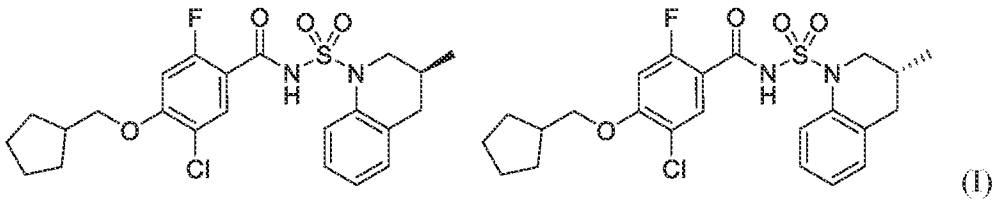
Example 15: 5-chloro-4-(cyclopentylmethoxy)-*N*-((3, 4-dihydro-1, 8-naphthyridin-1(2*H*)-yl)sulfonyl)-2-fluorobenzamide



(I)

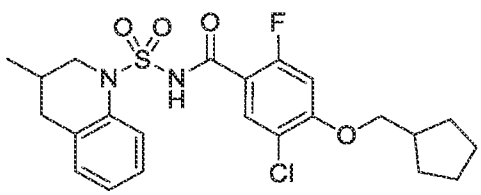
[0379] Following the procedure described in Example **14** and making non-critical variations as required to replace 1,2,3,4-tetrahydroquinoline with 1,2,3,4-tetrahydro-1,8-naphthyridine the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 - 7.95 (m, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.35 - 7.25 (m, 1H), 6.91 (d, J = 13.2 Hz, 1H), 6.75 - 6.65 (m, 1H), 3.98 - 3.85 (m, 4H), 2.72 - 2.63 (m, 2H), 2.35 - 2.24 (m, 1H), 1.90 - 1.81 (m, 2H), 1.80 - 1.70 (m, 2H), 1.64 - 1.48 (m, 4H), 1.39 - 1.28 (m, 2H). LCMS (ESI) m/z: 468.1 $[M+H]^+$.

Example 16 and Example 17: (*S*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-methyl-3,4-dihydroquinolin-1(2*H*)-yl)sulfonyl)benzamide and (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-methyl-3,4-dihydroquinolin-1(2*H*)-yl)sulfonyl)benzamide



(I)

Step 1: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-methyl-3,4-dihydroquinolin-1(2*H*)-yl)sulfonyl)benzamide

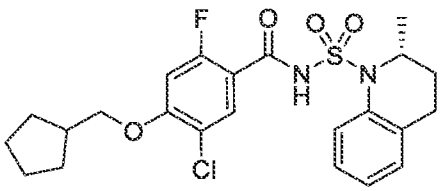


[0380] Following the procedure described in **Example 14** and making non-critical variations as required to replace 1,2,3,4-tetrahydroquinoline with 3-methyl-1,2,3,4-tetrahydroquinoline, the title compound was obtained as a white solid. LCMS (ESI) m/z: 481.2 $[M+H]^+$.

Step 2: (*S*)-4-(3-(dimethylamino)-3-phenethylpiperidin-1-yl)-2-fluoro-*N*-(pyrimidin-4-yl)benzenesulfonamide and (*R*)-4-(3-(dimethylamino)-3-phenethylpiperidin-1-yl)-2-fluoro-*N*-(pyrimidin-4-yl)benzenesulfonamide

[0381] 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-methyl-3,4-dihydroquinolin-1(2*H*)-yl)sulfonyl)benzamide (140 mg, 0.29 mmol) was separated by using chiral SFC (Chiralpak IG (250 mm * 30 mm, 10 um), Supercritical CO_2 / EtOH + Heptane = 95/5; 25 mL/min) to afford (*S*)-4-(3-(dimethylamino)-3-phenethylpiperidin-1-yl)-2-fluoro-*N*-(pyrimidin-4-yl)benzenesulfonamide (26 mg, first peak) as a white solid and (*R*)-4-(3-(dimethylamino)-3-phenethylpiperidin-1-yl)-2-fluoro-*N*-(pyrimidin-4-yl)benzenesulfonamide (24 mg, second peak) as a white solid. Absolute configuration was arbitrarily assigned to each enantiomer. Example **16**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.49 (s, 1H), 7.62 - 7.55 (m, 2H), 7.21 - 7.08 (m, 3H), 7.01 - 6.95 (m, 1H), 4.08 - 4.04 (m, 1H), 4.00 (d, J = 6.8 Hz, 2H), 3.40 - 3.37 (m, 1H), 2.84 - 2.79 (m, 1H), 2.44 - 2.27 (m, 2H), 2.11 - 2.04 (m, 1H), 1.80 - 1.72 (m, 2H), 1.65 - 1.49 (m, 4H), 1.37 - 1.29 (m, 2H), 1.03 (d, J = 6.4 Hz, 3H). LCMS (ESI) m/z: 481.2 $[M+H]^+$. Example **17**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.50 (s, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 7.2 Hz, 1H), 7.20 (d, J = 12 Hz, 1H), 7.17 - 7.11 (m, 2H), 7.02 - 6.98 (m, 1H), 4.08 - 4.04 (m, 1H), 4.00 (d, J = 6.8 Hz, 2H), 3.40 - 3.37 (m, 1H), 2.85 - 2.79 (m, 1H), 2.44 - 2.37 (m, 1H), 2.36 - 2.28 (m, 1H), 2.12 - 2.04 (m, 1H), 1.80 - 1.72 (m, 2H), 1.63 - 1.50 (m, 4H), 1.37 - 1.29 (m, 2H), 1.03 (d, J = 6.8 Hz, 3H). LCMS (ESI) m/z: 481.2 $[M+H]^+$.

Example 18: (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methyl-3,4-dihydroquinolin-1(2*H*)-yl)sulfonyl)benzamide

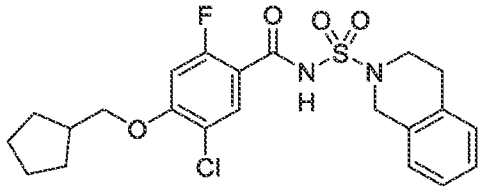


(I)

[0382] Following the procedure described in Example **14** and making non-critical variations as required to replace 1,2,3,4-tetrahydroquinoline with 2-methyl-1,2,3,4-tetrahydroquinoline, 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-[(2-methyl-3,4-dihydro-2*H*-quinolin-1-yl)sulfonyl]benzamide (420 mg, 0.87 mmol) was obtained as a white solid. The enantiomers were separated using chiral SFC (DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); Supercritical CO_2 / EtOH+0.1% NH_3•H_2O = 70/30; 70 mL/min) to afford the title compound (157 mg, first

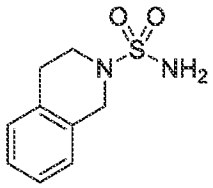
peak) as a white solid. Absolute configuration was arbitrarily assigned to each enantiomer. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.21 - 7.11 (m, 3H), 7.07 - 7.02 (m, 1H), 4.74 - 4.61 (m, 1H), 3.99 (d, J = 6.4 Hz, 2H), 2.70 - 2.60 (m, 2H), 2.38 - 2.25 (m, 1H), 2.24 - 2.14 (m, 1H), 1.82 - 1.69 (m, 2H), 1.65 - 1.48 (m, 5H), 1.38 - 1.27 (m, 2H), 1.18 (d, J = 6.4 Hz, 3H). LCMS (ESI) m/z: 481.2 $[M+H]^+$.

Example 19: 5-chloro-4-(cyclopentylmethoxy)-*N*-((3,4-dihydroisoquinolin-2(1*H*)-yl)sulfonyl)-2-fluorobenzamide



(I)

Step 1: 3,4-dihydroisoquinoline-2(1*H*)-sulfonamide

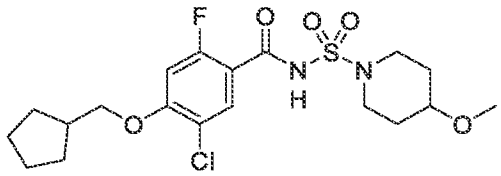


[0383] To a mixture of 1,2,3,4-tetrahydroisoquinoline (500 mg, 3.75 mmol) in 1,4-dioxane (26 mL) was added sulfamide (902 mg, 9.39 mmol). The mixture was stirred at 110 °C for 16 h under nitrogen atmosphere. After cooling to room temperature, the reaction was diluted with water (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (670 mg, crude) as a yellow solid that required no further purification. LCMS (ESI) m/z: 212.8 $[M+H]^+$.

Step 2: 5-chloro-4-(cyclopentylmethoxy)-*N*-((3,4-dihydroisoquinolin-2(1*H*)-yl)sulfonyl)-2-fluorobenzamide

[0384] Following the procedure described in Example **14** and making non-critical variations as required to replace 3,4-dihydroquinoline-1(2*H*)-sulfonamide with 3,4-dihydroisoquinoline-2(1*H*)-sulfonamide, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.97 (s, 1H), 7.59 (d, J = 7.2 Hz, 1H), 7.25 - 7.15 (m, 5H), 4.54 (s, 2H), 4.01 (d, J = 6.8 Hz, 2H), 3.61 (t, J = 5.6 Hz, 2H), 2.89 (t, J = 5.6 Hz, 2H), 2.39 - 2.27 (m, 1H), 1.80 - 1.72 (m, 2H), 1.65 - 1.48 (m, 4H), 1.40 - 1.29 (m, 2H). LCMS (ESI) m/z: 467.0 $[M+H]^+$.

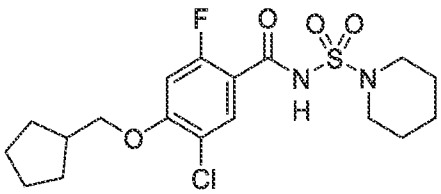
Example 20: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-methoxypiperidin-1-yl)sulfonyl)benzamide



(I)

[0385] Following the procedure described in Example **19** and making non-critical variations as required to replace 1,2,3,4-tetrahydroisoquinoline with 4-methoxypiperidine, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (s, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 12.4 Hz, 1H), 4.03 (d, J = 6.8 Hz, 2H), 3.53 - 3.37 (m, 3H), 3.23 (s, 3H), 3.19 - 3.12 (m, 2H), 2.38 - 2.30 (m, 1H), 1.88 - 1.73 (m, 4H), 1.64 - 1.49 (m, 6H), 1.40 - 1.32 (m, 2H). LCMS (ESI) m/z: 449.0 $[M+H]^+$.

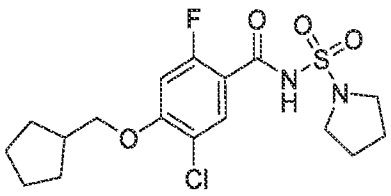
Example 21: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(piperidin-1-ylsulfonyl)benzamide



(I)

[0386] Following the procedure described in Example **19** and making non-critical variations as required to replace 1,2,3,4-tetrahydroisoquinoline with piperidine, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.77 (s, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.23 (d, J = 12.0 Hz, 1H), 4.03 (d, J = 6.8 Hz, 2H), 3.30 - 3.21 (m, 4H), 2.40 - 2.28 (m, 1H), 1.84 - 1.71 (m, 2H), 1.68 - 1.59 (m, 2H), 1.59 - 1.52 (m, 6H), 1.51 - 1.43 (m, 2H), 1.41 - 1.29 (m, 2H). LCMS (ESI) m/z: 419.0 $[M+H]^+$.

Example 22: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(pyrrolidin-1-ylsulfonyl)-benzamide

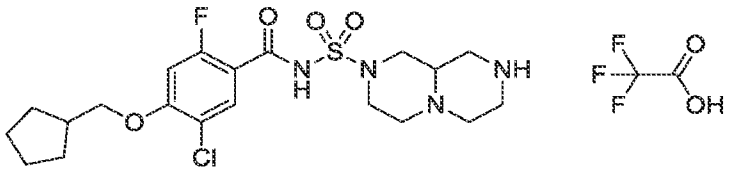


(I)

[0387] Following the procedure described in Example **19** and making non-critical variations as required to replace 1,2,3,4-tetrahydroisoquinoline with pyrrolidine, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.71 (d, J = 8.0 Hz,

1H), 7.21 (d, *J* = 12.4 Hz, 1H), 4.02 (d, *J* = 6.8 Hz, 2H), 3.43 - 3.37 (m, 4H), 2.36 - 2.31 (m, 1H), 1.85 - 1.81 (m, 4H), 1.80 - 1.73 (m, 2H), 1.67 - 1.59 (m, 2H), 1.58 - 1.51 (m, 2H) , 1.40 - 1.30(m, 2H). LCMS (ESI) m/z: 405.2 $[M+H]^+$.

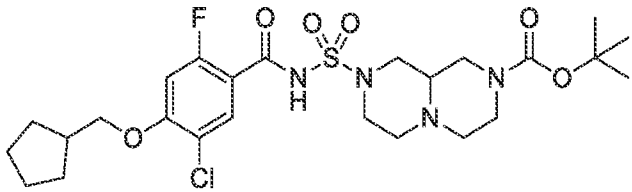
Example 23: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((octahydro-2H-pyrazino[1,2-a]pyrazin-2-yl)sulfonyl)benzamide



(I)

[0388] (This compound may also be referred to as: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((hexahydro-1H-pyrazino[1,2-a]pyrazin-2(6H)-yl)sulfonyl)benzamide 2,2,2-trifluoroacetate.)

Step 1: *tert*-butyl 8-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)hexahydro-1*H*-pyrazino[1,2-*a*]pyrazine-2(6*H*)-carboxylate



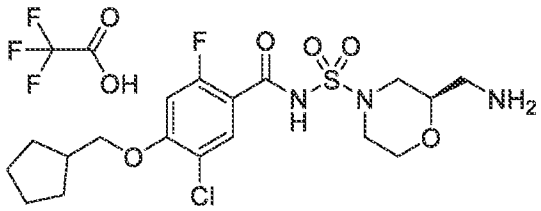
[0389] Following the procedure described in Example **19** and making non-critical variations as required to replace 1,2,3,4-tetrahydroisoquinoline with *tert*-butyl hexahydro-1*H*-pyrazino[1,2-a]pyrazine-2(6*H*)-carboxylate, the title compound was obtained as yellow oil. LCMS (ESI) m/z: 575.1 $[M+H]^+$.

Step 2: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((hexahydro-1*H*-pyrazino[1,2-a]pyrazin-2(6*H*)-yl)sulfonyl)benzamide 2,2,2-trifluoroacetate

[0390] To a stirred solution of *tert*-butyl 8-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)hexahydro-1*H*-pyrazino[1,2-*a*]pyrazine-2(6*H*)-carboxylate (310 mg, 0.54 mmol) in DCM (4 mL) was added 2,2,2-trifluoroacetic acid (2 mL, 23.24 mmol). The mixture was stirred at room temperature for 1 h. The mixture was concentrated in vacuo. The crude residue was purified by reverse phase chromatography (acetonitrile 30 - 60% / (0.075% 2,2,2-trifluoroacetic acid) in water) to afford the title compound (103 mg, 32%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.97 - 8.60 (m, 2H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 12.4 Hz, 1H), 4.03 (d, *J* = 6.8 Hz, 2H), 3.71 - 3.60 (m, 2H), 3.36 - 3.24 (m, 2H), 3.10

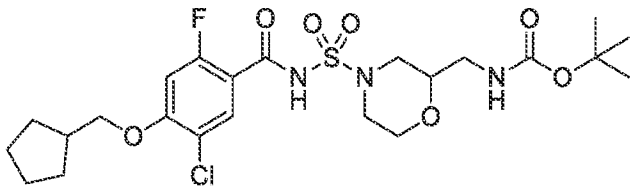
- 2.93 (m, 1H), 2.92 - 2.83 (m, 2H), 2.80 - 2.60 (m, 2H), 2.41 - 2.30 (m, 2H), 2.27 - 2.18 (m, 1H), 1.85 - 1.70 (m, 2H), 1.68 - 1.49 (m, 4H), 1.42 - 1.28 (m, 2H). LCMS (ESI) m/z: 475.1 $[M+H]^+$.

Example 24: (*R*)-*N*-((2-(aminomethyl)morpholino)sulfonyl)-5-chloro-4-(cyclopentyl-methoxy)-2-fluorobenzamide 2,2,2-trifluoroacetate



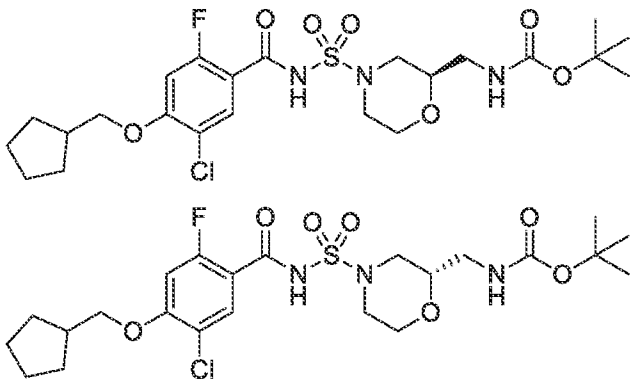
(I)

a. **Step 1: *tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)-sulfamoyl)morpholin-2-yl)methyl)carbamate**



[0391] Following the procedure described in Example **19** and making non-critical variations as required to replace 1,2,3,4-tetrahydroisoquinoline with *tert*-butyl (morpholin-2-ylmethyl)carbamate, the title compound was obtained as a white solid. LCMS (ESI) m/z: 450.2 $[M-100+H]^+$.

Step 2: (*R*)-*tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)carbamate and (*S*)-*tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)-morpholin-2-yl)methyl)carbamate



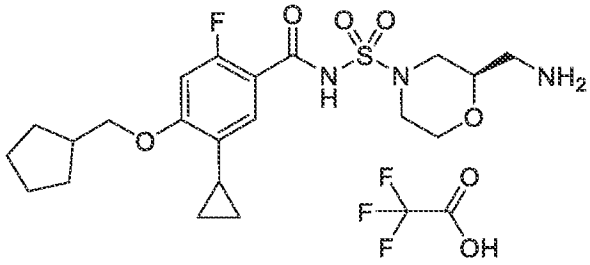
[0392] *tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl) morpholin-2-yl)methyl)carbamate (100 mg, 0.18 mmol) was separated by using chiral SFC (Chiralpak AD (250 mm * 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% $NH_3 \cdot H_2O$ = 65/35; 70 mL/min) to afford (*R*)-*tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-

fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)carbamate (40 mg, first peak) and (*S*)-*tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl) morpholin-2-yl)methyl)carbamate (30 mg, second peak). Absolute configuration was arbitrarily assigned to each enantiomer. LCMS (ESI) m/z: 450.2 $[M-100+H]^+$.

Step 3: (*R*)-*N*-((2-(aminomethyl)morpholino)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide 2,2,2-trifluoroacetate

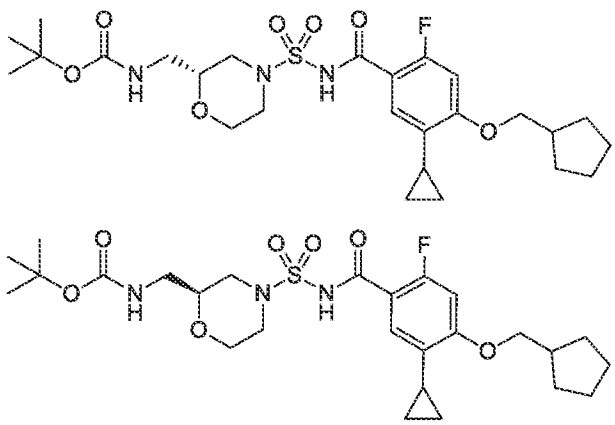
[0393] Following the procedure described in Example **23** and making non-critical variations as required to replace *tert*-butyl 8-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)hexahydro-1*H*-pyrazino[1,2-*a*]pyrazine-2(6*H*)-carboxylate with (*R*)-*tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)carbamate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 7.95 - 7.84 (s, 3H), 7.75 (d, J = 7.2 Hz, 1H), 7.24 (d, J = 12.4 Hz, 1H), 4.03 (d, J = 6.8 Hz, 2H), 4.10 - 3.96 (m, 1H), 3.72 - 3.65 (m, 2H), 3.58 - 3.48 (m, 2H), 3.15 - 2.99 (m, 2H), 2.93 - 2.76 (m, 2H), 2.40 - 2.28 (m, 1H), 1.85 - 1.70 (m, 2H), 1.69 - 1.45 (m, 4H), 1.42 - 1.29 (m, 2H). LCMS (ESI) m/z: 450.2 $[M+H]^+$.

Example 25: (R)-*N*-((2-(aminomethyl)morpholino)sulfonyl)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzamide 2,2,2-trifluoroacetate



(I)

a. **Step 1: (*R*)-*tert*-butyl ((4-(*N*-(4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)carbamate and (*S*)-*tert*-butyl ((4-(*N*-(4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)carbamate**

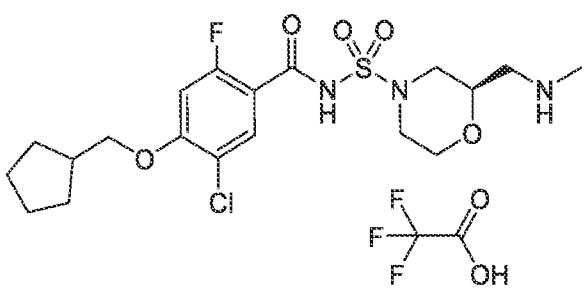


[0394] Following the procedure described in Example **19** and making non-critical variations as required to replace 1,2,3,4-tetrahydroisoquinoline with *tert*-butyl (morpholin-2-ylmethyl)carbamate and replace 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid with 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid, the title compound was obtained as yellow oil. *Tert*-butyl ((4-(*N*-(4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)carbamate (230 mg, 0.41 mmol) was separated by using chiral SFC (Chiralpak AD (250 mm * 30 mm, 10 μm), Supercritical CO_2 / MeOH + 0.1% $NH_3 \cdot H_2O$ = 55/45; 60 mL/min) to afford (*R*)-*tert*-butyl ((4-(*N*-(4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)carbamate (110 mg, first peak) and (*S*)-*tert*-butyl ((4-(*N*-(4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)carbamate (90 mg, second peak) both as yellow oil. Absolute configuration was arbitrarily assigned to each enantiomer. LCMS (ESI) m/z: 578.1 $[M+Na]^+$.

Step 2: (R)-*N*-((2-(aminomethyl)morpholino)sulfonyl)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzamide 2,2,2-trifluoroacetate

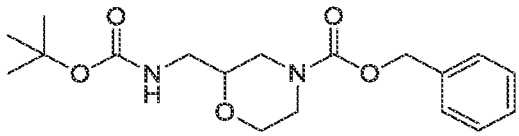
[0395] Following the procedure described in Example **23** and making non-critical variations as required to replace 8-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)hexahydro-1*H*-pyrazino[1,2-*a*]pyrazine-2(6*H*)-carboxylate with (*R*)-*tert*-butyl ((4-(*N*-(4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)carbamate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (s, 1H), 7.96 - 7.80 (m, 3H), 7.11 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 12.8 Hz, 1H), 4.05 - 3.97 (m, 1H), 3.96 (d, J = 6.8 Hz, 2H), 3.74 - 3.62 (m, 2H), 3.58 - 3.48 (m, 2H), 3.16 - 2.97 (m, 2H), 2.94 - 2.76 (m, 2H), 2.40 - 2.28 (m, 1H), 2.07 - 1.94 (m, 1H), 1.85 - 1.72 (m, 2H), 1.68 - 1.48 (m, 4H), 1.45 - 1.29 (m, 2H), 0.94 - 0.84 (m, 2H), 0.72 - 0.62 (m, 2H). LCMS (ESI) m/z: 456.2 $[M+H]^+$.

Example 26: (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-((methylamino) methyl)morpholino)sulfonyl) benzamide 2,2,2-trifluoroacetate



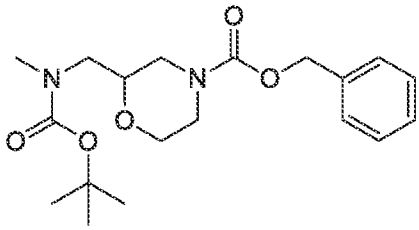
(I)

Step 1: Benzyl 2-(((*tert*-butoxycarbonyl)amino)methyl)morpholine-4-carboxylate



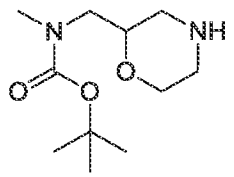
[0396] To a solution of *tert*-butyl *N*-(morpholin-2-ylmethyl)carbamate (500 mg, 2.31 mmol) and benzyl chloroformate (0.39 mL, 2.77 mmol) in DCM (16 mL) was added DIPEA (1.0 mL, 5.78 mmol) dropwise at 0 °C. After stirring for 0.5 h, the reaction was stirred at room temperature for 16 h. The reaction was diluted with water (30 mL) and extracted with DCM (30 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 60% EtOAc in petroleum ether) to afford the title compound (715 mg, 88%) as yellow oil. LCMS (ESI) m/z: 251.2 $[M-100+H]^+$.

Step 2: benzyl 2-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)morpholine-4-carboxylate



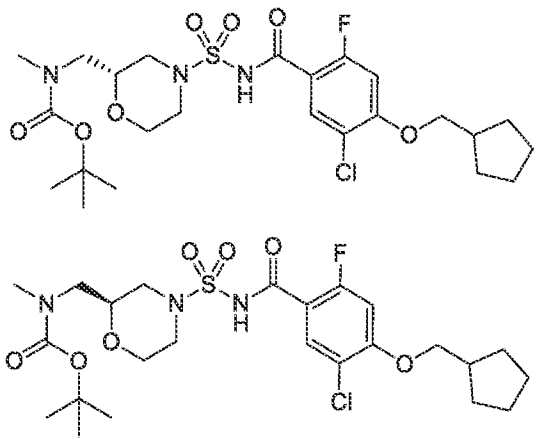
[0397] To a solution of benzyl 2-(((*tert*-butoxycarbonyl) amino) methyl) morpholine-4-carboxylate (405 mg, 1.16 mmol) in THF (11 mL) was added NaH (92 mg, 2.31 mmol) at room temperature under nitrogen atmosphere. After the mixture was stirred for 30 min, MeI (600 mg, 3.32 mmol) was added slowly at room temperature under nitrogen atmosphere. The mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL), extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (415 mg, crude) as yellow oil that required no further purification. LCMS (ESI) m/z: 265.2 $[M-100+H]^+$.

Step 3: *tert*- butyl methyl(morpholin-2-ylmethyl)carbamate



[0398] To a solution of benzyl 2-[[*tert*-butoxycarbonyl(methyl)amino]methyl]morpholine-4-carboxylate (415 mg, 1.14 mmol) in EtOAc (16 mL) was added 10% Pd/C (606 mg, 0.57 mmol). The mixture was stirred at room temperature for 1 h under hydrogen atmosphere (15 psi). The mixture was filtered and the filtrate was concentrated in vacuo to afford the title compound (235 mg, crude) as yellow oil that required no further purification.

Step 4: (*R*)-*tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl) sulfamoyl) morpholin-2-yl)methyl)(methyl)carbamate and (*S*)-*tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl) sulfamoyl) morpholin-2-yl)methyl)(methyl)carbamate



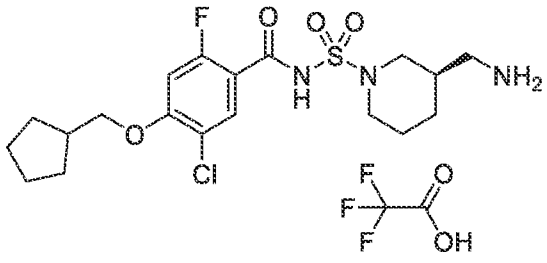
[0399] Following the procedure described in Example **24** and making non-critical variations as required to replace *tert*-butyl (morpholin-2-ylmethyl)carbamate with *tert*-butyl methyl (morpholin-2-ylmethyl)carbamate, *tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)(methyl)carbamate was obtained as a white solid. *Tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)(methyl)carbamate (190 mg, 0.34 mmol) was separated by using chiral SFC (Chiralpak AD (250 mm * 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% $NH_3 \cdot H_2O$ = 55/45; 80 mL/min) to afford (*R*)-*tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)(methyl)carbamate (60 mg, first peak) and (*S*)-*tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)(methyl)carbamate (60 mg, second peak) both as a white solid. Absolute configuration was arbitrarily assigned to each enantiomer. LCMS (ESI) m/z: 464.2 $[M-100+H]^+$.

Step 5: (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-((methylamino)methyl)morpholino)sulfonyl)benzamide 2,2,2-trifluoroacetate

[0400] To a stirred solution of (*R*)-*tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)(methyl)carbamate (60 mg, 0.11 mmol) in DCM

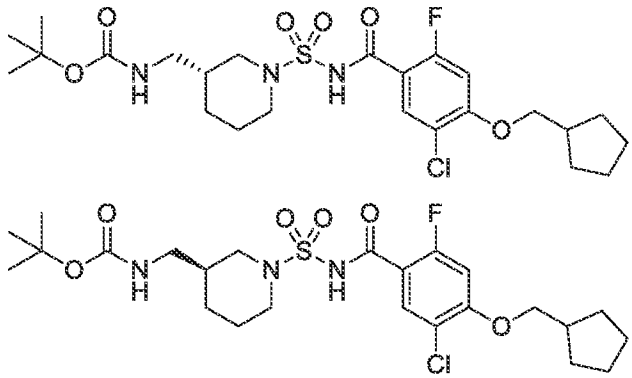
(1 mL) was added 2,2,2-trifluoroacetic acid (0.5 mL) at room temperature for 1 h. The mixture was concentrated in vacuo. The crude residue was purified by reverse phase chromatography (acetonitrile 25 - 55% / 0.2 % HCOOH in water) to afford the title compound (15 mg, 25%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (s, 2H), 7.74 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 12.4 Hz, 1H), 3.98 - 3.89 (m, 3H), 3.76 - 3.68 (m, 1H), 3.58 - 3.50 (m, 1H), 3.43 - 3.36 (m, 2H), 3.28 - 3.25 (m, 1H), 3.14 - 3.08 (m, 1H), 3.05 - 2.96 (m, 1H), 2.83 - 2.74 (m, 1H), 2.55 (s, 3H), 2.34 - 2.23 (m, 1H), 1.82 - 1.72 (m, 2H), 1.67 - 1.48 (m, 4H), 1.40 - 1.29 (m, 2H). LCMS (ESI) m/z: 464.2 $[M+H]^+$.

Example 27: (*R*)-*N*-((3-(aminomethyl)piperidin-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide 2,2,2-trifluoroacetate



(I)

Step 1: (*R*)-*tert*-butyl ((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-3-yl)methyl)carbamate, and (*S*)-*tert*-butyl ((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-3-yl)methyl)carbamate



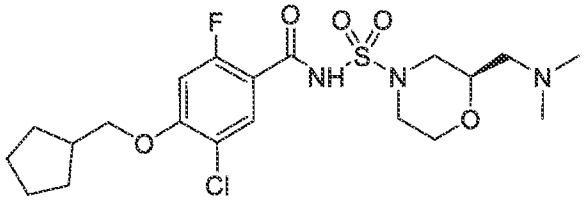
[0401] Following the procedure described in Example **24** and making non-critical variations as required to replace *tert*-butyl (morpholin-2-ylmethyl)carbamate with *tert*-butyl (piperidin-3-ylmethyl)carbamate, *tert*-butyl ((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-3-yl)methyl)carbamate was obtained as a white solid. *tert*-butyl ((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-3-yl)methyl)carbamate (180 mg, 0.33 mmol) was separated by using chiral SFC (DAICEL CHIRALCEL OD-H (250 mm * 30 mm, 5 um); Supercritical CO_2 / EtOH + 0.1% NH_3•H_2O = 50/50; 70 ml/min) to afford (*R*)-*tert*-butyl ((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-

fluorobenzoyl)sulfamoyl)piperidin-3-yl)methyl)carbamate (60 mg, first peak) and (*S*)-*tert*-butyl ((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-3-yl)methyl)carbamate (60 mg, second peak) both as a white solid. Absolute configuration was arbitrarily assigned to each enantiomer. LCMS (ESI) m/z: 448.0 $[M-100+H]^+$.

Step 2: (*R*)-*N*-((3-(aminomethyl)piperidin-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide 2,2,2-trifluoroacetate

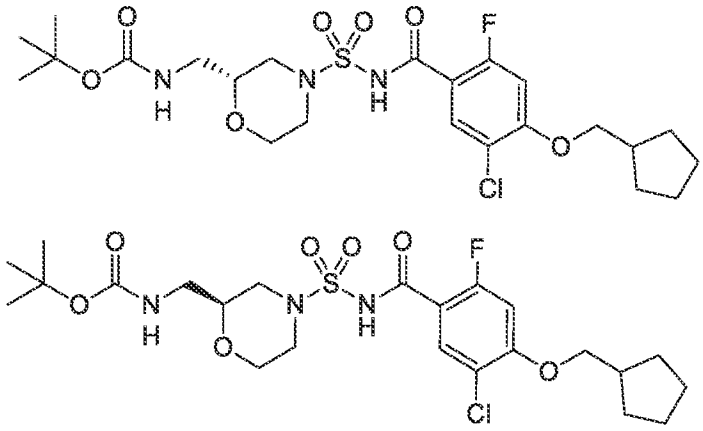
[0402] Following the procedure described in Example **24** and making non-critical variations as required to replace (*R*)-*tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)carbamate with (*R*)-*tert*-butyl ((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-3-yl)methyl)carbamate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 7.83 (s, 3H), 7.71 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 12.8 Hz, 1H), 4.02 (d, J = 7.2 Hz, 2H), 3.77 (d, J = 10.0 Hz, 1H), 3.55 (d, J = 12.0 Hz, 1H), 2.92 - 2.70 (m, 4H), 2.36 - 2.27 (m, 1H), 1.84 - 1.72 (m, 5H), 1.66 - 1.30 (m, 7H), 1.19 - 1.08 (m, 1H). LCMS (ESI) m/z: 448.0 $[M+H]^+$.

Example 28: (*R*)-5-chloro-4-(cyclopentylmethoxy)-*N*-((2-((dimethylamino)methyl)-morpholino)sulfonyl)-2-fluorobenzamide



(I)

Step 1: (*R*)-*tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl) morpholin-2-yl)methyl)carbamate and (*S*)-*tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)carbamate

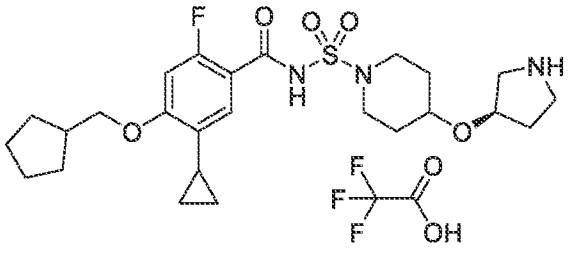


[0403] Following the procedure described in Example **25** and making non-critical variations as required to replace 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid, *tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)carbamate was obtained as a white solid. *tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)carbamate (220 mg, 0.4 mmol) was separated by using chiral SFC (DAICEL CHIRALCEL OD-H (250 mm * 30 mm, 5 um), Supercritical CO_2 / EtOH + 0.1% $NH_3 \cdot H_2O$ = 65/35; 60 mL/min) to afford (*R*)-*tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)carbamate (40 mg, first peak) and (*S*)-*tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)carbamate (60 mg, second peak) both as a white solid. Absolute configuration was arbitrarily assigned to each enantiomer. LCMS (ESI) m/z: 450.2 $[M-100+H]^+$.

Step 2: (*R*)-5-chloro-4-(cyclopentylmethoxy)-*N*-((2-((dimethylamino)methyl)morpholino)sulfonyl)-2-fluorobenzamide

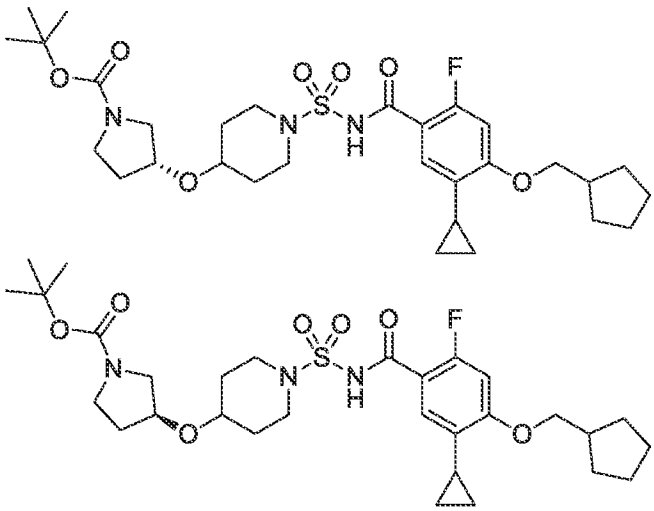
[0404] Following the procedure described in Example **9** and making non-critical variations as required to replace *tert*-butyl 3-((1-(*N*-(5-cyclopropyl-4-(cyclopropylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)azetidine-1-carboxylate with (*R*)-*tert*-butyl ((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)morpholin-2-yl)methyl)carbamate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 12.0 Hz, 1H), 3.95 (d, J = 6.8 Hz, 2H), 3.94 - 3.75 (m, 2H), 3.65 - 3.56 (m, 1H), 3.50 - 3.35 (m, 4H), 3.10 - 3.20 (m, 2H), 2.73 (s, 6H), 2.37 - 2.28 (m, 1H), 1.80 - 1.72 (m, 2H), 1.66 - 1.50 (m, 4H), 1.40 - 1.31 (m, 2H). LCMS (ESI) m/z: 478.0 $[M+H]^+$.

Example 29: (*R*)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((4-(pyrrolidin-3-yloxy)piperidin-1-yl)sulfonyl)benzamide 2,2,2-trifluoroacetate



(I)

Step 1: (*R*)-*tert*-butyl 3-((1-(*N*-(4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate and (*S*)-*tert*-butyl 3-((1-(*N*-(4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate

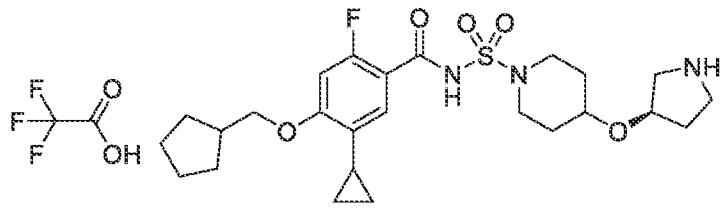


[0405] Following the procedure described in Example **25** and making non-critical variations as required to replace *tert*-butyl (morpholin-2-ylmethyl)carbamate with *tert*-butyl 3-(piperidin-4-yloxy)pyrrolidine-1-carboxylate, *tert*-butyl 3-((1-(*N*-(4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate was obtained as yellow oil. *Tert*-butyl 3-((1-(*N*-(4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate (120 mg, 0.23 mmol) was separated by using chiral SFC (Chiralpak AD (250 mm * 30 mm, 10 um), Supercritical CO_2 / IPA + 0.1% $NH_3 \cdot H_2O$ = 65/35; 70 mL/min) to afford (*R*)-*tert*-butyl 3-((1-(*N*-(4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate (60 mg, first peak) and (*S*)-*tert*-butyl 3-((1-(*N*-(4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate (50 mg, second peak) both as yellow oil. Absolute configuration was arbitrarily assigned to each enantiomer. LCMS (ESI) m/z: 510.3 $[M-100+H]^+$.

Step 2: (*R*)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((4-(pyrrolidin-3-yloxy)piperidin-1-yl)sulfonyl)benzamide 2,2,2-trifluoroacetate

[0406] Following the procedure described in Example **1** and making non-critical variations as required to replace *tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)azetidine-1-carboxylate with (*R*)-*tert*-butyl 3-((1-(*N*-(4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.64 (s, 1H), 9.08 - 8.72 (m, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 13.2 Hz, 1H), 4.40 - 4.30 (m, 1H), 3.95 (d, J = 6.8 Hz, 2H), 3.63 - 3.47 (m, 3H), 3.28 - 3.05 (m, 6H), 2.40 - 2.27 (m, 1H), 2.06 - 1.84 (m, 5H), 1.84 - 1.72 (m, 2H), 1.70 - 1.43 (m, 6H), 1.42 - 1.29 (m, 2H), 0.94 - 0.84 (m, 2H), 0.70 - 0.61 (m, 2H). LCMS (ESI) m/z: 510.1 $[M+H]^+$.

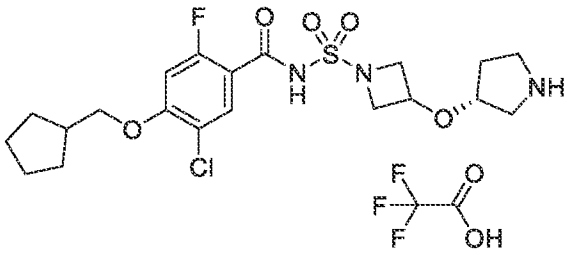
Example 30: (*S*)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluoro-*N*-((4-(pyrrolidin-3-yloxy)piperidin-1-yl)sulfonyl)benzamide 2,2,2-trifluoroacetate



(I)

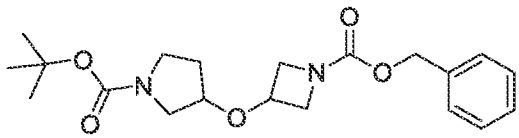
[0407] Following the procedure described in Example **29** and making non-critical variations as required to replace (*R*)-*tert*-butyl 3-((1-(*N*-(4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate with (*S*)-*tert*-butyl 3-((1-(*N*-(4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.64 (s, 1H), 9.02 - 8.76 (m, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 13.2 Hz, 1H), 4.40 - 4.30 (m, 1H), 3.95 (d, J = 6.8 Hz, 2H), 3.63 - 3.47 (m, 3H), 3.28 - 3.05 (m, 6H), 2.40 - 2.27 (m, 1H), 2.06 - 1.84 (m, 5H), 1.84 - 1.72 (m, 2H), 1.70 - 1.43 (m, 6H), 1.42 - 1.29 (m, 2H), 0.94 - 0.84 (m, 2H), 0.70 - 0.61 (m, 2H). LCMS (ESI) m/z: 510.1 $[M+H]^+$.

Example 31: (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-(pyrrolidin-3-yloxy)azetidin-1-yl)sulfonyl)benzamide 2,2,2-trifluoroacetate



(I)

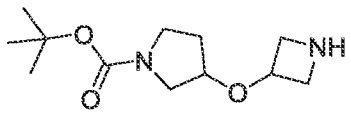
Step 1: *tert*-butyl 3-((1-((benzyloxy)carbonyl)azetidin-3-yl)oxy)pyrrolidine-1-carboxylate



[0408] A mixture of benzyl 3-hydroxyazetidine-1-carboxylate (2.73 g, 13.18 mmol) and NaH (527 mg, 13.18 mmol, 60% in mineral oil) in DMF (35 mL) was stirred at 0 °C for 1 h. *Tert*-butyl 3-(tosyloxy)pyrrolidine-1-carboxylate (3.00 g, 8.79 mmol) was added at 0 °C. The mixture was stirred at room temperature for 16 h. The reaction was diluted with water (50 mL) and extracted with DCM (50 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by reverse phase chromatography (acetonitrile 25 - 60% / 0.05% $NH_3{\cdot}H_2O$ + 10 mM NH_4HCO_3 in

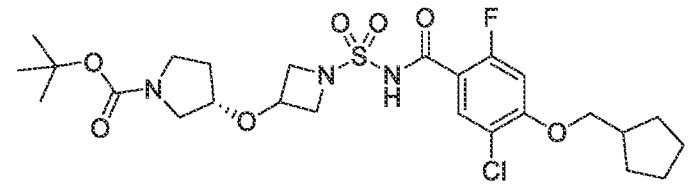
water) to afford the title compound (150 mg, 5%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.27 (m, 5H), 5.09 (s, 2H), 4.34 - 4.28 (m, 1H), 4.21 - 4.17 (m, 2H), 3.99 (s, 1H), 3.93 - 3.89 (m, 2H), 3.46 - 3.33 (m, 4H), 1.93 (s, 2H), 1.46 (s, 9H). LCMS (ESI) m/z: 277.2 [M-100+H]$^+$.

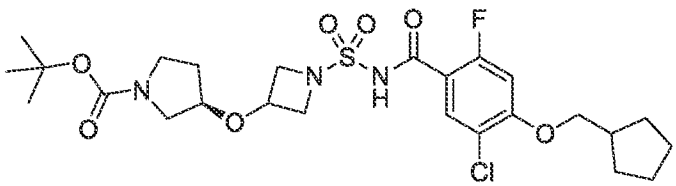
Step 2: *tert*-butyl 3-(azetidin-3-yloxy)pyrrolidine-1-carboxylate



[0409] To a solution of *tert*-butyl 3-((1-((benzyloxy)carbonyl)azetidin-3-yl)oxy)pyrrolidine-1-carboxylate (150 mg, 0.4 mmol) in EtOAc (9 mL), 10% Pd/C (212 mg, 0.2 mmol) was added. The mixture was stirred at room temperature for 16 h under hydrogen atmosphere (15 psi). The reaction was filtered and concentrated in vacuo to afford the title compound (95 mg, crude) as colorless oil that required no further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 - 4.23 (m, 1H), 3.92 (s, 1H), 3.67 - 3.52 (m, 3H), 3.35 - 3.19 (m, 6H), 1.83 - 1.78 (m, 2H), 1.36 (s, 9H).

Step 3: (*S*)-*tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)-sulfamoyl)azetidin-3-yl)oxy)pyrrolidine-1-carboxylate and (*R*)-*tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)azetidin-3-yl)oxy)pyrrolidine-1-carboxylate





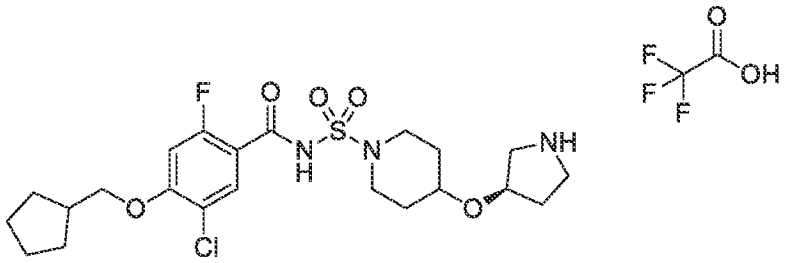
[0410] Following the procedure described in Example **19** and making non-critical variations as required to replace 1,2,3,4-tetrahydroisoquinoline with *tert*-butyl 3-(azetidin-3-yloxy)pyrrolidine-1-carboxylate, *tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)azetidin-3-yl)oxy)pyrrolidine-1-carboxylate was obtained as a white solid. *tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)azetidin-3-yl)oxy)pyrrolidine-1-carboxylate (110 mg, 0.19 mmol) was separated by using chiral SFC (Chiralpak AD (250 mm * 30 mm, 10 um), Supercritical NH_3•H_2O / MeOH + Heptane = 55/45; 80 mL/min) to afford (*S*)-*tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-

fluorobenzoyl)sulfamoyl)azetidin-3-yl)oxy)pyrrolidine-1-carboxylate (40 mg, first peak) and (*R*)-*tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)azetidin-3-yl)oxy)pyrrolidine-1-carboxylate (40 mg, second peak) both as a white solid. Absolute configuration was arbitrarily assigned to each enantiomer. LCMS (ESI) m/z: 476.2 $[M-100+H]^+$.

Step 4: (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-(pyrrolidin-3-yloxy)azetidin-1-yl)sulfonyl)benzamide 2,2,2-trifluoroacetate

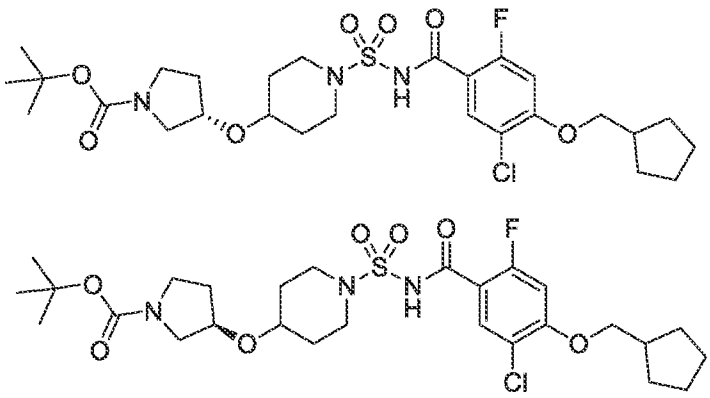
[0411] Following the procedure described in Example **1** and making non-critical variations as required to replace *tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)azetidine-1-carboxylate with (*R*)-*tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)azetidin-3-yl)oxy)pyrrolidine-1-carboxylate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 2H), 7.76 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 12.4 Hz, 1H), 4.42 - 4.36 (m, 1H), 4.24 - 4.19 (m, 3H), 4.03 (d, J = 6.8 Hz, 2H), 3.96 - 3.92 (m, 2H), 3.24 - 3.14 (m, 4H), 2.38 - 2.29 (m, 1H), 1.97 - 1.92 (m, 2H), 1.81 - 1.74 (m, 2H), 1.66 - 1.49 (m, 4H), 1.39 - 1.31 (m, 2H). LCMS (ESI) m/z: 476.1 $[M+H]^+$.

Example 36: (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(pyrrolidin-3-yloxy)piperidin-1-yl)sulfonyl)benzamide 2,2,2-trifluoroacetate



(I)

a. **Step 1: (*S*)-*tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate and (*R*)-*tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate**

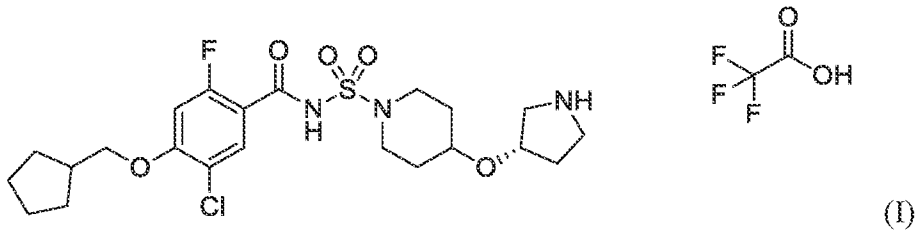


[0412] Following the procedure described in Example **29** and making non-critical variations as required to replace 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid, *tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate was obtained as a white solid. *Tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate (320 mg, 0.53 mmol) was separated by using chiral SFC (DAICEL CHIRALPAK AD-H (250 mm * 30 mm, 5 um), Supercritical CO_2 / EtOH + 0.1% $NH_3 \cdot H_2O$ = 65/35; 60 mL/min) to afford (*S*)-*tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate (160 mg, first peak) as a white solid and (*R*)-*tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate (130 mg, second peak) as a white solid. Absolute configuration was arbitrarily assigned to each enantiomer. LCMS (ESI) m/z: 504.2 $[M-100+H]^+$.

Step 2: (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(pyrrolidin-3-yloxy)piperidin-1-yl)sulfonyl)benzamide 2,2,2-trifluoroacetate

[0413] Following the procedure described in Example **1** and making non-critical variations as required to replace *tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)-sulfamoyl)piperidin-4-yl)oxy)azetidine-1-carboxylate with (*R*)-*tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.81 (s, 1H), 8.99 - 8.70 (m, 2H), 7.69 (d, J = 7.2 Hz, 1H), 7.23 (d, J = 12.4 Hz, 1H), 4.38 - 4.32 (m, 1H), 4.03 (d, J = 6.4 Hz, 2H), 3.56 - 3.51 (m, 2H), 3.24 - 3.11 (m, 6H), 2.42 - 2.28 (m, 1H), 2.02 - 1.93 (m, 2H), 1.92 - 1.84 (m, 2H), 1.82 - 1.73 (m, 2H), 1.68 - 1.59 (m, 2H), 1.58 - 1.44 (m, 4H), 1.41 - 1.30 (m, 2H). LCMS (ESI) m/z: 504.2 $[M+H]^+$.

Example 37: (*S*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(pyrrolidin-3-yloxy)-piperidin-1-yl)sulfonyl)benzamide 2,2,2-trifluoroacetate

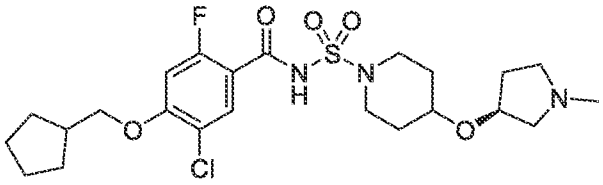


(I)

[0414] Following the procedure described in Example **36** and making non-critical variations as required to replace (*R*)-*tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate with (*S*)-*tert*-butyl 3-((1-

(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.81 (s, 1H), 9.03 - 8.73 (m, 2H), 7.69 (d, J = 7.2 Hz, 1H), 7.23 (d, J = 12.4 Hz, 1H), 4.38 - 4.31 (m, 1H), 4.03 (d, J = 6.8 Hz, 2H), 3.60 - 3.50 (m, 2H), 3.22 - 3.10 (m, 6H), 2.39 - 2.29 (m, 1H), 2.01 - 1.93 (m, 2H), 1.92 - 1.84 (m, 2H), 1.82 - 1.73 (m, 2H), 1.66 - 1.58 (m, 2H), 1.57 - 1.43 (m, 4H), 1.40 - 1.30 (m, 2H). LCMS (ESI) m/z: 504.2 $[M+H]^+$.

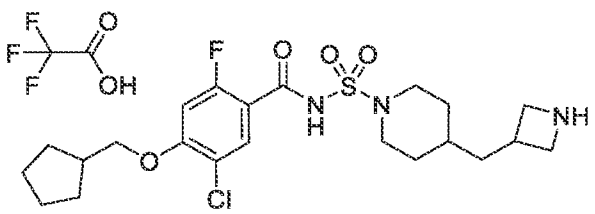
Example 38: (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((1-methylpyrrolidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide



(I)

[0415] Following the procedure described in Example **1** and making non-critical variations as required to replace *N*-((4-(azetidin-3-yloxy)piperidin-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide with (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(pyrrolidin-3-yloxy)piperidin-1-yl)sulfonyl)benzamide 2,2,2-trifluoroacetate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 12.4 Hz, 1H), 4.35 (m, 1H), 3.96 (d, J = 6.8 Hz, 2H), 3.25 - 3.12 (m, 7H), 2.80 - 2.70 (m, 5H), 2.36 - 2.31 (m, 1H), 2.23 - 2.16 (m, 1H), 1.95 - 1.85 (m, 3H), 1.79 - 1.73 (m, 2H), 1.65 - 1.52 (m, 4H), 1.45 - 1.33 (m, 4H). LCMS (ESI) m/z: 518.2 $[M+H]^+$.

Example 40: *N*-((4-(azetidin-3-ylmethyl)piperidin-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide 2,2,2-trifluoroacetate

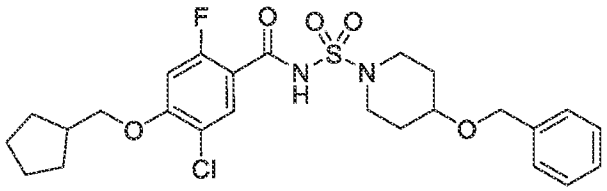


(I)

[0416] Following the procedure described in Example **1** and making non-critical variations as required to replace *tert*-butyl 3-(piperidin-4-yloxy)azetidine-1-carboxylate with *tert*-butyl 3-(piperidin-4-ylmethyl)azetidine-1-carboxylate (Reference: WO2017/95758), the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68 (d, J = 7.6 Hz, 1H), 7.00 (d, J = 12.8 Hz, 1H), 4.11 (t, J = 10.0 Hz, 2H), 4.01 (d, J = 6.4 Hz, 2H), 3.93 - 3.84 (m, 2H), 3.77 (t, J = 8.4 Hz, 2H), 3.11 - 3.00 (m, 1H), 2.98 - 2.88 (m, 2H), 2.48 - 2.38 (m, 1H), 1.92 - 1.84 (m,

2H), 1.74 - 1.63 (m, 7H), 1.49 - 1.38 (m, 3H), 1.34 - 1.23 (m, 3H). LCMS (ESI) m/z: 488.1 $[M+H]^+$.

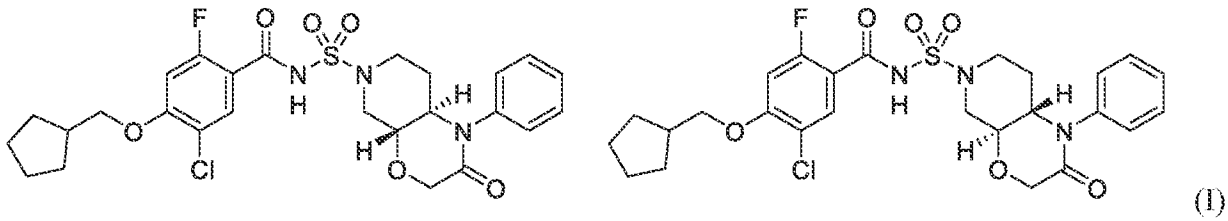
Example 41: *N*-((4-(benzyloxy)piperidin-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

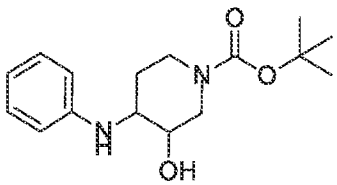
[0417] Following the procedure described in Example **19** and making non-critical variations as required to replace 1,2,3,4-tetrahydroisoquinoline with 4-(benzyloxy)piperidine, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.35 - 7.19 (m, 6H), 4.50 (s, 2H), 4.01 (d, J = 6.4 Hz, 2H), 3.57 - 3.46 (m, 3H), 3.22 - 3.06 (m, 2H), 2.36 - 2.30 (m, 1H),1.94 - 1.85(m, 2H), 1.81 - 1.73 (m, 2H), 1.67 - 1.57 (m, 4H), 1.56 - 1.49 (m, 2H), 1.38 - 1.33 (m, 2H). LCMS (ESI) m/z: 525.2 $[M+H]^+$.

Example 44 and Example 45: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(((*4aR,8aR*)-2-oxo-1-phenylhexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazin-6(7*H*)-yl)sulfonyl)benzamide, and 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(((*4aS,8aS*)-2-oxo-1-phenylhexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazin-6(7*H*)-yl)sulfonyl)benzamide



(I)

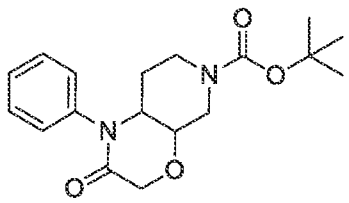
Step 1: *trans-tert*-butyl 3-hydroxy-4-(phenylamino)piperidine-1-carboxylate



[0418] To a solution of *tert*-butyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (2 g, 10.04 mmol) in 1,2-dichloroethane (40 mL) was added aniline (1 g, 11.04 mmol) and *tri*-(trifluoromethylsulfonyloxy)scandium (0.74 g, 1.51 mmol). The reaction was stirred at room temperature under nitrogen atmosphere for 16 h. The mixture was concentrated in vacuo and the crude residue was purified by silica gel chromatography (solvent gradient: 0 - 15% EtOAc in

petroleum ether) to afford the title compound (800 mg, 27%) as a white solid. LCMS (ESI) m/z: 237.2 $[M-56+H]^+$.

Step 2: *trans-tert*-butyl 2-oxo-1-phenylhexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazine-6(7*H*)-carboxylate



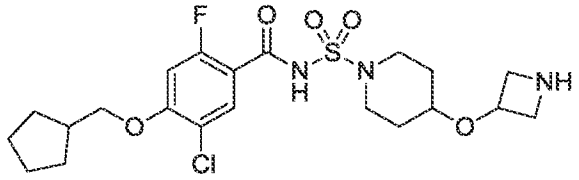
[0419] To a solution of NaH (657 mg, 16.42 mmol, 60% in mineral oil) in THF (15 mL) was added ethyl bromoacetate (0.91 mL, 8.21 mmol) at 0 °C. The mixture was stirred for 0.5 h. *Trans-tert*-butyl 3-hydroxy-4-(phenylamino)piperidine-1-carboxylate (800 mg, 2.74 mmol) was added to the mixture at 0 °C and the reaction was stirred at room temperature for 16 h. The reaction was quenched with saturated anqueous NH_4Cl (20 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 40% EtOAc in petroleum ether) to afford the title compound (450 mg, 50%) as a yellow solid. LCMS (ESI) m/z: 333.2 $[M+H]^+$.

Step 3: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(((*4aR,8aR*)-2-oxo-1-phenylhexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazin-6(7*H*)-yl)sulfonyl)benzamide and 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(((*4aS,8aS*)-2-oxo-1-phenylhexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazin-6(7*H*)-yl)sulfonyl)benzamide

[0420] Following the procedure described in Example **42** and making non-critical variations as required to replace *trans*-1-methylhexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazin-2(3*H*)-one with *trans-tert*-butyl 2-oxo-1-phenylhexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazine-6(7*H*)-carboxylate, *trans*-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-oxo-1-phenylhexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazin-6(7*H*)-yl)sulfonyl)benzamide was obtained as a yellow solid. *Trans*-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-oxo-1-phenylhexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazin-6(7*H*)-yl)sulfonyl)benzamide (60 mg, 0.09 mmol) was separated by using chiral SFC (Chiralpak AD (250 mm * 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% $NH_3 \cdot H_2O$ = 60/40; 70 mL/min) to afford 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(((*4aR,8aR*)-2-oxo-1-phenylhexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazin-6(7*H*)-yl)sulfonyl)benzamide (5 mg, second peak) as a white solid. Absolute configuration was arbitrarily assigned. Example **44:** ^1H NMR (400 MHz, DMSO-d_6) δ 11.99 (s, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.47 - 7.37 (m, 2H), 7.36 - 7.29 (m, 1H), 7.24 (d, J = 7.6 Hz, 2H), 7.21 - 7.24 (m, 1H), 4.45 - 4.25 (m, 2H), 4.02 (d, J = 6.4 Hz, 2H), 3.94 - 3.72 (m, 3H),

3.67 - 3.57 (m, 1H), 3.04 - 2.76 (m, 2H), 2.38 - 2.25 (m, 1H), 1.85 - 1.70 (m, 2H), 1.69 - 1.49 (m, 4H), 1.46 - 1.27 (m, 4H). LCMS (ESI) m/z: 565.9 $[M+H]^+$.

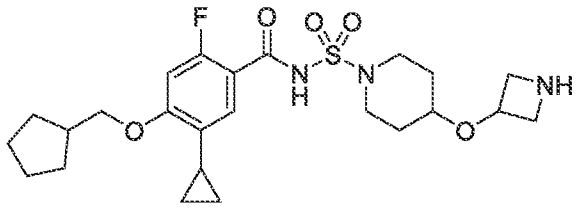
Example 46: *N*-((4-(azetidin-3-yloxy)piperidin-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

[0421] Following the procedure described in Example **1** and making non-critical variations as required to replace *tert*-butyl 3-hydroxyazetidine-1-carboxylate with *tert*-butyl 3-hydroxyazetidine-1-carboxylate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 12.4 Hz, 1H), 4.50 - 4.30 (m, 1H), 4.05 - 3.96 (m, 2H), 3.96 - 3.94 (m, 1H), 3.90 (d, J = 6.8 Hz, 2H), 3.74 - 3.67 (m, 2H), 3.26 - 3.23 (m, 2H), 2.74 - 2.65 (m, 2H), 2.38 - 2.27 (m, 1H), 1.85 - 1.71 (m, 4H), 1.67 - 1.50 (m, 4H), 1.46 - 1.29 (m, 4H). LCMS (ESI) m/z: 490.2 $[M+H]^+$.

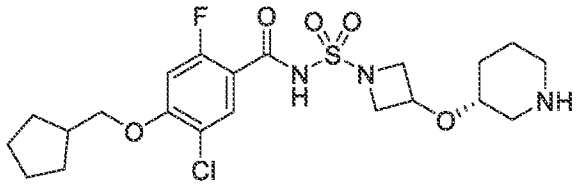
Example 47: *N*-((4-(azetidin-3-yloxy)piperidin-1-yl)sulfonyl)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzamide



(I)

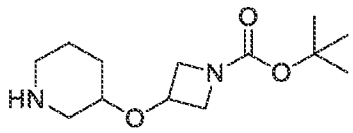
[0422] Following the procedure described in Example **46** and making non-critical variations as required to replace 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid with 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 (d, J = 8.8 Hz, 1H), 6.64 (d, J = 12.4 Hz, 1H), 4.51 - 4.41 (m, 1H), 4.16 - 4.07 (m, 2H), 3.87 (d, J = 6.8 Hz, 2H), 3.84 - 3.74 (m, 2H), 3.45 - 3.37 (m, 4H), 2.78 - 2.65 (m, 1H), 2.37 - 2.27 (m, 1H), 2.03 - 1.94 (m, 1H), 1.84 - 1.72 (m, 4H), 1.68 - 1.49 (m, 4H), 1.48 - 1.31 (m, 4H), 0.90 - 0.81 (m, 2H), 0.57 - 0.49 (m, 2H). LCMS (ESI) m/z: 496.1 $[M+H]^+$.

Example 48: (*S*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-(piperidin-3-yloxy) azetidin-1-yl) sulfonyl)benzamide



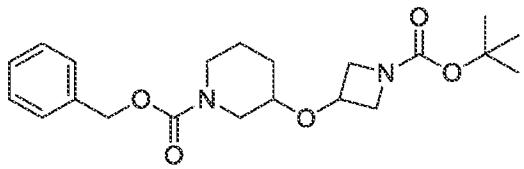
(I)

Step 1: *tert*-butyl 3-(piperidin-3-yloxy)azetidine-1-carboxylate



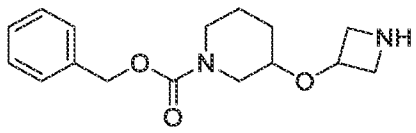
[0423] Following the procedure described in Example **1** and making non-critical variations as required to replace *tert*-butyl 3-hydroxyazetidine-1-carboxylate and pyridin-4-ol with *tert*-butyl 3-hydroxyazetidine-1-carboxylate and pyridin-3-ol, the title compound was obtained as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.34 - 4.23 (m, 1H), 4.08 - 3.99 (m, 2H), 3.75 - 3.84 (m, 2H), 3.29 - 3.20 (m, 1H), 3.04 - 2.95 (m, 1H), 2.84 - 2.75 (m, 1H), 2.65 - 2.50 (m, 2H), 1.87 - 1.77 (m, 2H), 1.76 - 1.65 (m, 1H), 1.47 - 1.42 (m, 1H), 1.40 (s, 9H).

Step 2: benzyl 3-((1-(*tert*-butoxycarbonyl)azetidin-3-yl)oxy)piperidine-1-carboxylate



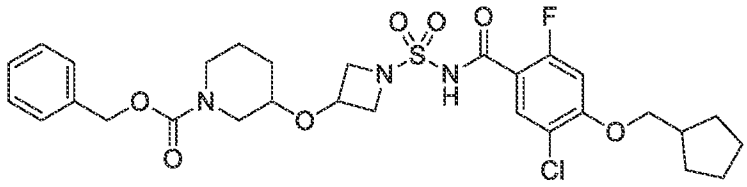
[0424] To a solution of *tert*-butyl 3-(piperidin-3-yloxy)azetidine-1-carboxylate (500 mg, 1.95 mmol) in DCM (15 mL) was added DIPEA (0.97 mL, 5.85 mmol) and benzyl chloroformate (0.4 mL, 2.93 mmol). The mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) and extracted with DCM (50 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (620 mg, crude) as yellow oil that required no further purification. LCMS (ESI) m/z: 291.2 $[M-100+H]^+$.

Step 3: benzyl 3-(azetidin-3-yloxy)piperidine-1-carboxylate



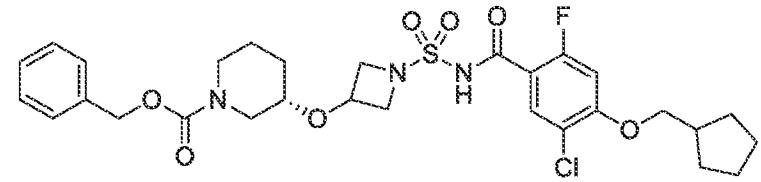
[0425] Following the procedure described in Example **2** and making non-critical variations as required to replace *tert*-butyl 4-(cyclopentylmethoxy)-2-fluoro-5-methylbenzoate with benzyl 3-((1-(*tert*-butoxycarbonyl)azetidin-3-yl)oxy)piperidine-1-carboxylate, the title compound was obtained as yellow oil. LCMS (ESI) m/z: 291.2 $[M+H]^+$.

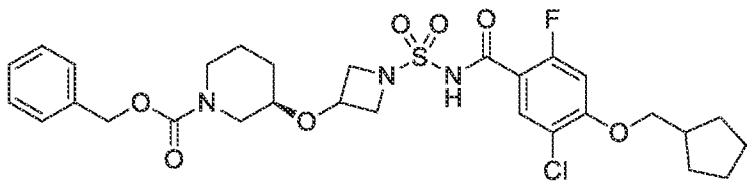
Step 4: benzyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)azetidin-3-yl)oxy)piperidine-1-carboxylate



[0426] Following the procedure described in Example **1** and making non-critical variations as required to replace *tert*-butyl 3-(piperidin-4-yloxy)azetidine-1-carboxylate with benzyl 3-(azetidin-3-yloxy)piperidine-1-carboxylate, the title compound was obtained as yellow oil. LCMS (ESI) m/z: 624.1 $[M+H]^+$.

Step 5: (*S*)-benzyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)-sulfamoyl)azetidin-3-yl)oxy)piperidine-1-carboxylate, and (*R*)-benzyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)-azetidin-3-yl)oxy)piperidine-1-carboxylate





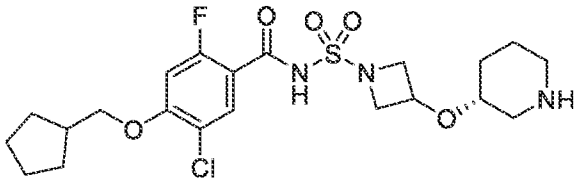
[0427] benzyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)azetidin-3-yl)oxy)piperidine-1-carboxylate (150 mg, 0.24 mmol) was separated by using chiral SFC daicel chiralpak IG (250 mm * 30 mm,10 um; Supercritical CO_2 / *i*-PrOH + 0.1% $NH_3 \cdot H_2O$ = 50/50; 80 mL/min) to afford (*S*)-benzyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)azetidin-3-yl)oxy)piperidine-1-carboxylate (70 mg, first peak) and (*R*)-benzyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)azetidin-3-yl)oxy)piperidine-1-carboxylate (70 mg, second peak) both as

a white solid. Absolute configuration was arbitrarily assigned to each enantiomer. LCMS (ESI) m/z: 624.1 $[M+H]^+$.

Step 6: (*S*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-(piperidin-3-yloxy)azetidin-1-yl)sulfonyl)benzamide

[0428] A solution of (*S*)-benzyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)-sulfamoyl)azetidin-3-yl)oxy)piperidine-1-carboxylate (70 mg, 0.11 mmol) in DCM (1 mL) was added $PdCl_2$ (5 mg, 0.025 mmol). The mixture was stirred for 16 h under hydrogen atmosphere (15 psi) at room temperature. The resulting residue was purified by reverse phase chromatography (acetonitrile 25 - 55% / 0.2% formic acid in water) to afford the title compound (21 mg, 39%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 12.4 Hz, 1H), 4.34 - 4.24 (m, 1H), 3.95 (d, J = 6.8 Hz, 2H), 3.84 - 3.75 (m, 2H), 3.72 - 3.56 (m, 3H), 3.18 - 3.08 (m, 1H), 2.99 - 2.85 (m, 3H), 2.36 - 2.27 (m, 1H), 1.81 - 1.73 (m, 4H), 1.63 - 1.52 (m, 6H), 1.41 - 1.31 (m, 2H). LCMS (ESI) m/z: 490.1 $[M+H]^+$.

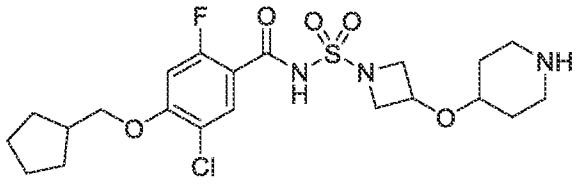
Example 49: (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-(piperidin-3-yloxy)-azetidin-1-yl)sulfonyl)benzamide



(I)

[0429] Following the procedure described in Example **48** and making non-critical variations as required to replace (*S*)-benzyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)azetidin-3-yl)oxy)piperidine-1-carboxylate with (*R*)-benzyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)azetidin-3-yl)oxy)piperidine-1-carboxylate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 12.4 Hz, 1H), 4.32 - 4.23 (m, 1H), 3.95 (d, J = 6.8 Hz, 2H), 3.83 - 3.75 (m, 2H), 3.72 - 3.62 (m, 3H), 3.16 - 3.09 (m, 1H), 2.99 - 2.85 (m, 3H), 2.36 - 2.27 (m, 1H), 1.81 - 1.74 (m, 4H), 1.64 - 1.51 (m, 6H), 1.41 - 1.30 (m, 2H). LCMS (ESI) m/z: 490.0 $[M+H]^+$.

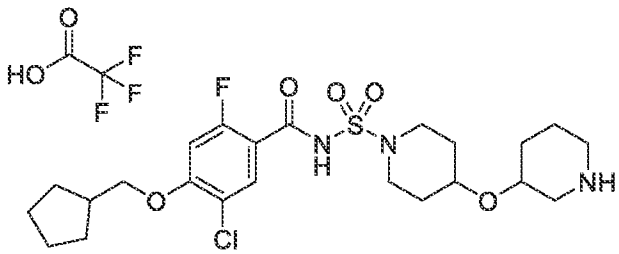
Example 50: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-(piperidin-4-yloxy) azetidin-1-yl)sulfonyl)benzamide



(I)

[0430] Following the procedure described in Example **31** and making non-critical variations as required to replace *tert*-butyl 3-hydroxypyrrolidine-1-carboxylate with *tert*-butyl 4-hydroxypiperidine-1-carboxylate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 12.4 Hz, 1H), 4.26 - 4.18 (m, 1H), 3.95 (d, J = 6.8 Hz, 2H), 3.79 - 3.73 (m, 2H), 3.67 - 3.61 (m, 2H), 3.30 - 3.25 (m, 1H), 3.19 - 3.14 (m, 1H), 2.97 - 2.88 (m, 2H), 2.37 - 2.27 (m, 1H), 1.94 - 1.85 (m, 2H), 1.82 - 1.75 (m, 2H), 1.66 - 1.52 (m, 6H), 1.40 - 1.33 (m, 2H), LCMS (ESI) m/z: 490.1 $[M+H]^+$.

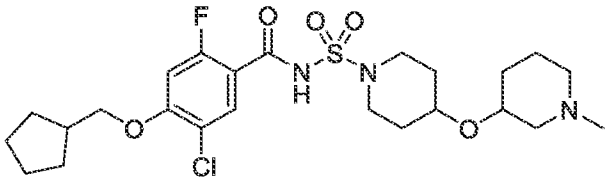
Example 51: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(piperidin-3-yloxy)piperidin-1-yl)sulfonyl)benzamide 2,2,2-trifluoroacetate



(I)

[0431] Following the procedure described in Example **1** and making non-critical variations as required to replace *tert*-butyl 3-hydroxyazetidine-1-carboxylate with *tert*-butyl 3-hydroxy-piperidine-1-carboxylate, the title compound was obtained as a white solid, assumed to be a mixture of enantiomers. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 8.55 (s, 1H), 8.27 (s, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.23 (d, J = 12.4 Hz, 1H), 4.03 (d, J = 6.8 Hz, 2H), 3.80 - 3.70 (m, 1H), 3.69 - 3.60 (m, 1H), 3.59 - 3.45 (m, 2H), 3.22 - 3.05 (m, 3H), 2.99 - 2.90 (m, 3H), 2.40 - 2.25 (m, 1H), 1.93 - 1.70 (m, 6H), 1.68 - 1.57 (m, 4H), 1.57 - 1.45 (m, 4H), 1.43 - 1.29 (m, 2H), LCMS (ESI) m/z: 518.1 $[M+H]^+$.

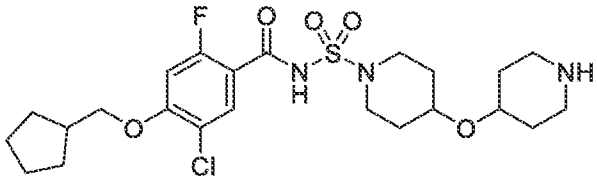
Example 52: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((1-methylpiperidin-3-yl)oxy)piperidin-1-yl)sulfonyl) benzamide



(I)

[0432] Following the procedure described in Example **1** and making non-critical variations as required to replace *N*-((4-(azetidin-3-yloxy)piperidin-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide with 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(piperidin-3-yloxy)piperidin-1-yl)sulfonyl)benzamide, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 12.0 Hz, 1H), 3.95 (d, J = 6.8 Hz, 2H), 3.75 - 3.68 (m, 1H), 3.60 - 3.40 (m, 3H), 3.21 - 3.05 (m, 2H), 2.97 - 2.89 (m, 1H), 2.85-2.72 (m, 3H), 2.60 (s, 3H), 2.37 - 2.25 (m, 1H), 1.89 - 1.69 (m, 6H), 1.67 - 1.49 (m, 6H), 1.48 - 1.26 (m, 4H), LCMS (ESI) m/z: 532.1 $[M+H]^+$.

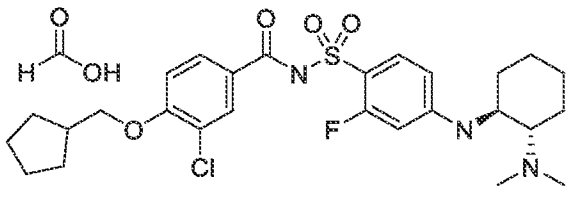
Example 53: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(piperidin-4-yloxy) piperidin-1-yl)sulfonyl) benzamide



(I)

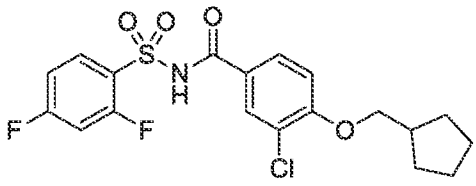
[0433] Following the procedure described in Example **1** and making non-critical variations as required to replace *tert*-butyl 3-hydroxyazetidine-1-carboxylate with *tert*-butyl 4-(piperidin-4-yloxy) piperidine-1-carboxylate, the title compound was obtained as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 12.0 Hz, 1H), 3.98 (d, J = 6.4 Hz, 2H), 3.78 - 3.62 (m, 1H), 3.61 - 3.48 (m, 1H), 3.46 -3.40 (m, 2H), 3.21 - 3.08 (m, 2H), 3.03 - 2.86 (m, 4H), 2.36 - 2.29 (m, 1H), 1.96 - 1.86 (m, 2H), 1.85 - 1.76 (m, 4H), 1.66 - 1.57 (m, 4H), 1.56 - 1.52 (m, 2H), 1.49 - 1.40 (m, 2H), 1.35 - 1.25 (m, 2H). LCMS (ESI) m/z: 518.2 $[M+H]^+$.

Example 57: 3-chloro-4-(cyclopentylmethoxy)-*N*-((4-(((1*S*,2*S*)-2-(dimethylamino)-cyclohexyl)amino)-2-fluorophenyl)sulfonyl)benzamide formate



(I)

Step 1: 3-chloro-4-(cyclopentylmethoxy)-*N*-((2,4-difluorophenyl)sulfonyl)benzamide

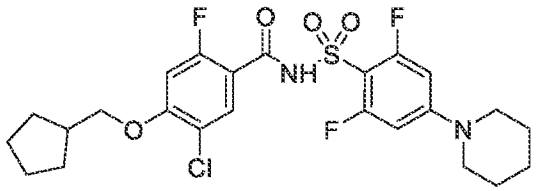


[0434] To a mixture of DMAP (126 mg, 1.04 mmol) and EDCI (99 mg, 0.52 mmol) in DCM (4 mL) was added 3-chloro-4-(cyclopentylmethoxy)benzoic acid (132 mg, 0.52 mmol) and 2,4-difluorobenzenesulfonamide (100 mg, 0.52 mmol). The mixture was stirred at room temperature for 16 h under nitrogen atmosphere. The reaction was diluted with water (10 mL) and extracted with EtOAc (15 mL x 3).The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by prep-TLC (DCM:MeOH = 20:1) to afford the title compound (180 mg, 0.42 mmol) as colorless oil. LCMS (ESI) m/z: 430.0 $[M+H]^+$.

Step 2: 3-chloro-4-(cyclopentylmethoxy)-*N*-((4-(((1*S*,2*S*)-2-(dimethylamino)-cyclohexyl)amino)-2-fluorophenyl)sulfonyl)benzamide formate

[0435] Following the procedure described in Example **55** and making non-critical variations as required to replace *N*-((5-chloro-2,4-difluorophenyl)sulfonyl)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzamide with 3-chloro-4-(cyclopentylmethoxy)-*N*-((2,4-difluorophenyl)sulfonyl)benzamide, the title compound was obtained as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 8.78 (s, 1H), 7.98 (s, 1H), 7.90 - 7.80 (m, 1H), 7.65 (t, J = 8.8 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 6.77 (s, 1H), 6.69 - 6.50 (m, 2H), 4.02 (d, J = 6.8 Hz, 2H), 3.90 - 3.75 (m, 1H), 3.20 - 3.09 (m, 1H), 2.76 (d, J = 4.4 Hz, 3H), 2.59 (d, J = 4.8 Hz, 3H), 2.40 - 2.30 (m, 1H), 2.11 - 2.01 (m, 1H), 2.00 - 1.91 (m, 1H), 1.87 - 1.72 (m, 3H), 1.67 - 1.50 (m, 5H), 1.46 - 1.25 (m, 5H), 1.21 - 1.08 (m, 1H). LCMS (ESI) m/z: 552.1 $[M+H]^+$.

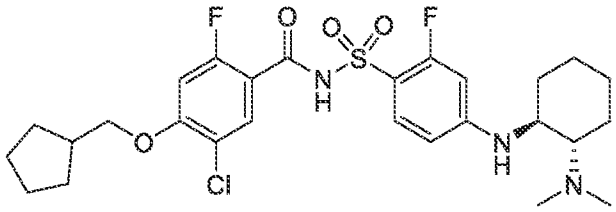
Example 58: 5-chloro-4-(cyclopentylmethoxy)-*N*-((2,6-difluoro-4-(piperidin-1-yl)phenyl)-sulfonyl)-2-fluorobenzamide



(I)

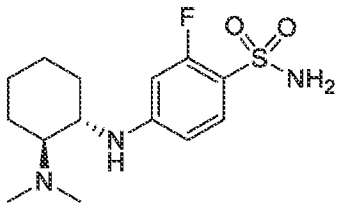
[0436] Following the procedure described in Example **57** and making non-critical variations as required to replace 2,4-difluorobenzenesulfonamide with 2,4,6-trifluorobenzenesulfonamide, replace 3-chloro-4-(cyclopentylmethoxy)benzoic acid with 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid, and replace (1*S*,2*S*)-*N*1,*N*1-dimethylcyclohexane-1,2-diamine with piperidine, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 12.6 Hz, 1H), 6.70 (d, J = 14.0 Hz, 2H), 4.02 (d, J = 6.8 Hz, 2H), 3.42 - 3.39 (m, 4H), 2.37 - 2.27 (m, 1H), 1.83 - 1.73 (m, 2H), 1.64 - 1.48 (m, 10H), 1.40 - 1.30 (m, 2H). LCMS (ESI) m/z: 531.2 $[M+H]^+$.

Example 59: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-(((1*S*,2*S*)-2-(dimethylamino)-cyclohexyl)amino)-2-fluorophenyl)sulfonyl)-2-fluorobenzamide



(I)

Step 1: 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzenesulfonamide

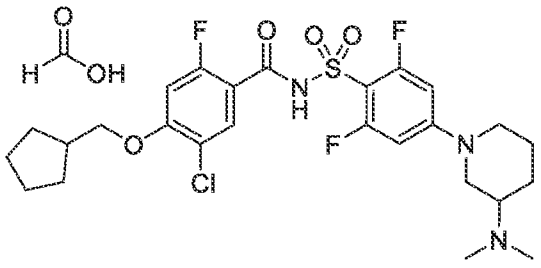


[0437] A solution of (1*S*,2*S*)-N^1,N^1-dimethylcyclohexane-1,2-diamine (162 mg, 1.1 mmol), 2,4-difluorobenzenesulfonamide (200 mg, 1.0 mmol) and DIPEA (0.3 mL, 1.7 mmol) in DMSO (3 mL) was stirred at 80 °C for 16 h. After cooling to room temperature, the reaction was diluted with EtOAc (100 mL), and washed with brine (50 mL x 5). The organic lawyer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to afford the title compound (60 mg, 0.19 mmol) as yellow oil. LCMS (ESI) m/z: 316.1 $[M+H]^+$.

Step 2: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-(((1*S*,2*S*)-2-(dimethylamino)-cyclohexyl)amino)-2-fluorophenyl)sulfonyl)-2-fluorobenzamide

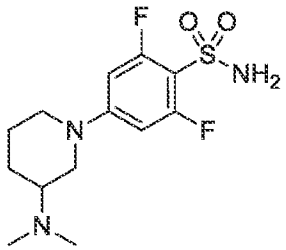
[0438] To a solution of 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzenesulfonamide (80 mg, 0.24 mmol) and DMAP (59 mg, 0.48 mmol) in DCM (2 mL) was added EDCI (51 mg, 0.26 mmol) and 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-benzoic acid (72 mg, 0.26 mmol). The reaction was stirred at room temperature for 2 h. The reaction was quenched with 10% aqueous citric acid (5 mL). The reaction was diluted with water (10 mL) and extracted with DCM (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 5% MeOH in DCM) to afford the title compound (40 mg, 28%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, J = 7.6 Hz, 1H), 7.55 - 7.48 (m, 1H), 6.94 (d, J = 12.4 Hz, 1H), 6.50 (s, 1H), 6.47 (s, 1H), 6.07 (d, J = 10.0 Hz, 1H), 3.94 (d, J = 6.8 Hz, 2H), 3.79 - 3.64 (m, 1H), 3.15 - 3.05 (m, 1H), 2.66 (s, 6H), 2.35 - 2.25 (m, 1H), 2.09 - 1.94 (m, 2H), 1.84 - 1.69(m, 3H), 1.63 - 1.14 (m, 11H). LCMS (ESI) m/z: 570.2 $[M+H]^+$.

Example 62: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-(3-(dimethylamino)piperidin-1-yl)-2,6-difluorophenyl)sulfonyl)-2-fluorobenzamide formate



(I)

Step 1: 4-(3-(dimethylamino)piperidin-1-yl)-2,6-difluorobenzenesulfonamide

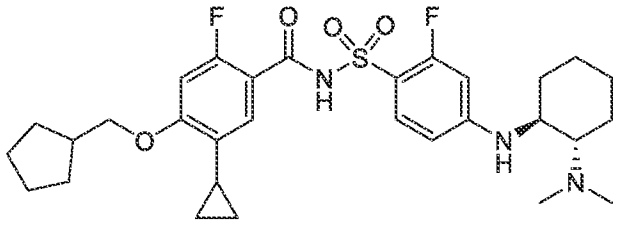


[0439] A solution of 3-dimethylaminopiperidine (35 mg, 0.27 mmol), 2,4,6-trifluoro-benzenesulfonamide (57 mg, 0.27 mmol) and DIPEA (0.36 mL, 2.18 mmol) in DMSO (1 mL) was stirred at 40 °C for 16 h. After cooling to room temperature, the reaction was diluted with EtOAc (60 mL), and washed with brine (30 mL x 5). The organic lawyer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by prep-TLC (DCM:MeOH = 10:1) to afford the title compound (20 mg, 16%) as a white solid. LCMS (ESI) m/z: 320.1 $[M+H]^+$.

Step 2: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-(3-(dimethylamino)piperidin-1-yl)-2,6-difluorophenyl)sulfonyl)-2-fluorobenzamide formate

[0440] Following the procedure described in Example **59** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzene-sulfonamide with 4-(3-(dimethylamino)piperidin-1-yl)-2,6-difluorobenzenesulfonamide and replace (1*S*,2*S*)-*N1*,*N1*-dimethylcyclohexane-1,2-diamine with *N*,*N*-dimethylpiperidin-3-amine, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 12.4 Hz, 1H), 6.57 (d, J = 12.4 Hz, 2H), 3.95 (d, J = 6.4 Hz, 3H), 3.78 - 3.73 (m, 1H), 3.13 - 2.94 (m, 2H), 2.86 - 2.75 (m, 8H), 2.35 - 2.28 (m, 1H), 2.07 - 1.95 (m, 1H), 1.78 - 1.72 (m, 3H), 1.61 - 1.51 (m, 6H), 1.39 - 1.30 (m, 2H). LCMS (ESI) m/z: 574.3 $[M+H]^+$.

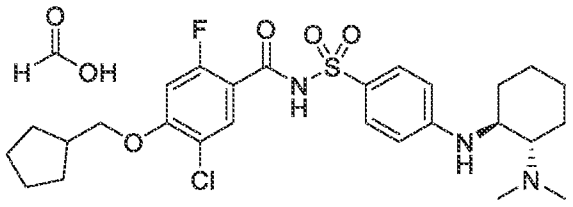
Example 63: 4-(cyclopentylmethoxy)-5-cyclopropyl-*N*-((4-(((1*S*,2*S*)-2-(dimethylamino)-cyclohexyl)amino)-2-fluorophenyl)sulfonyl)-2-fluorobenzamide



(I)

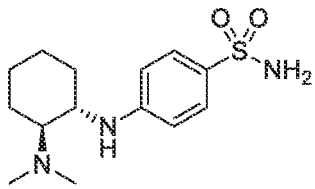
[0441] Following the procedure described in Example **59** and replace 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid with 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (t, J = 8.8 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 6.65 (d, J = 12.0 Hz, 1H), 6.52 - 6.34 (m, 2H), 5.99 (s, 1H), 3.87 (d, J = 6.8 Hz, 2H), 3.72 - 3.52 (m, 1H), 3.05 - 2.81 (m, 1H), 2.61 - 2.52 (m, 6H), 2.37 - 2.26 (m, 1H), 2.07 - 1.90 (m, 3H), 1.87 - 1.71 (m, 3H), 1.66 - 1.52 (m, 5H), 1.45 - 1.30 (m, 4H), 1.29 - 1.20 (m, 1H), 1.15 - 1.05 (m, 1H), 0.91 - 0.80 (m, 2H), 0.60 - 0.45 (m, 2H). LCMS (ESI) m/z: 576.1[M+H]$^+$.

Example 64: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-(((1*S*,2*S*)-2-(dimethylamino)-cyclohexyl)amino)phenyl)sulfonyl)-2-fluorobenzamide formate



(I)

Step 1: 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)benzenesulfonamide

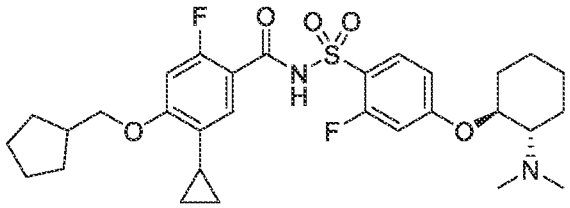


[0442] A solution of (1*S*,2*S*)-*N*1,*N*1-dimethylcyclohexane-1,2-diamine (811 mg, 5.71 mmol), 4-fluorobenzenesulfonamide (200 mg, 1.14 mmol) and DIPEA (737 mg, 5.71 mmol) in DMSO (1 mL) was stirred at 150 °C for 2 h under microwave. After cooling to room temperature, the reaction was diluted with EtOAc (60 mL), and washed with brine (30 mL x 5). The organic lawyer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to afford the title compound (125 mg, 15%) as a white solid. LCMS (ESI) m/z: 298.2 [M+H]$^+$.

Step 2: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-(((1*S*,2*S*)-2-(dimethylamino)-cyclohexyl)amino)phenyl)sulfonyl)-2-fluorobenzamide formate

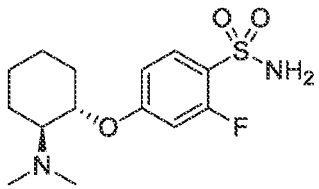
[0443] Following the procedure described in Example **59** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzene-sulfonamide with 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino) benzenesulfonamide as a white solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.27 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 12.4 Hz, 1H), 6.68 (d, *J* =8.8 Hz, 2H), 5.77 (s, 1H), 3.93 (d, *J* = 6.8 Hz, 2H), 3.70 - 3.58 (m, 1H), 3.12 - 3.07 (m, 1H), 2.63 (s, 6H), 2.34 - 2.26 (m, 1H), 2.03 - 1.93 (m, 2H), 1.92 - 1.68 (m, 3H), 1.67 - 1.39 (m, 6H), 1.38 - 1.21 (m, 4H), 1.19 - 1.07 (m, 1H). LCMS (ESI) m/z: 552.3 $[M+H]^+$.

Example 65: 4-(cyclopentylmethoxy)-5-cyclopropyl-*N*-((4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorophenyl)sulfonyl)-2-fluorobenzamide



(I)

Step 1: 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzenesulfonamide



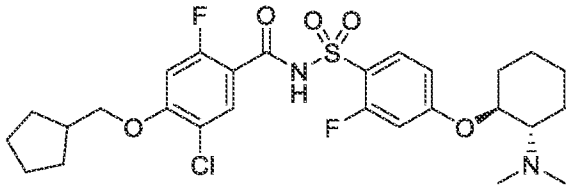
[0444] To a solution of thionylchloride (0.07 mL, 0.95 mmol) in DCM (2 mL) at 0 °C, 4-[(1*S*,2*S*)-2-(dimethylamino)cyclohexoxy]-2-fluoro-benzenesulfonic acid (100 mg, 0.32 mmol) and two drops of DMF were added. The mixture was stirred at room temperature for 2 h. Then NH_3•H_2O (0.1 mL) was added at 0 °C and the reaction was stirred at room temperature for 30 min. The solvent was concentrated in vacuo to afford the title compound (126 mg, crude) as colorless oil that required no further purification. LCMS (ESI) m/z: 317.2 $[M+H]^+$.

Step 2: 4-(cyclopentylmethoxy)-5-cyclopropyl-*N*-((4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorophenyl)sulfonyl)-2-fluorobenzamide

[0445] To a solution of 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzenesulfonamide in DCM (2 mL) was addded HATU (35 mg, 0.09 mmol), DIPEA (0.06 mL, 0.36 mmol) and 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluoro-benzoic acid (20 mg, 0.07 mmol). The mixture was stirred at room temperature for 16 h. The reaction was diluted with water

(30 mL), and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by reverse phase chromatography (acetonitrile 33 - 63% / 0.2% HCOOH in water) to afford the title compound (3 mg, 7%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 - 7.68 (m, 1H), 7.23 (d, J = 8.4 Hz, 1H), 6.96 - 6.82 (m, 2H), 6.65 (d, J = 11.6 Hz, 1H), 4.75 - 4.60 (m, 1H), 3.87 (d, J = 6.8 Hz, 2H), 3.25 - 3.15 (m, 1H), 2.67 (s, 6H), 2.36 - 2.29 (m, 1H), 2.25 - 2.12 (m, 1H), 2.06 - 1.92 (m, 2H), 1.86 - 1.73 (m, 2H), 1.71 - 1.23 (m, 12H), 0.90 - 0.80 (m, 2H), 0.57 - 0.48 (m, 2H). LCMS (ESI) m/z: 577.1 $[M+H]^+$.

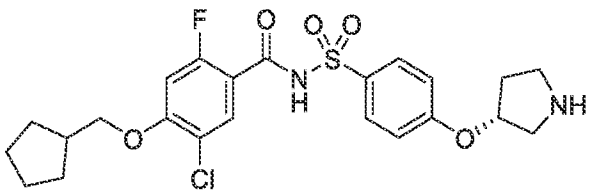
Example 66: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-(((1*S*,2*S*)-2-(dimethylamino)-cyclohexyl)oxy)-2-fluorophenyl)sulfonyl)-2-fluorobenzamide



(I)

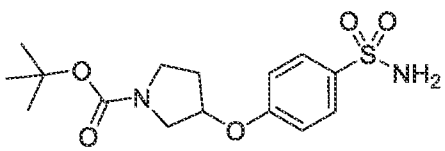
[0446] Following the procedure described in Example **65** and making non-critical variations as required to replace 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-benzoic acid, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1H), 7.81 - 7.69 (m, 2H), 7.03 - 6.88 (m, 3H), 4.81 - 4.63 (m, 1H), 3.95 (d, J = 6.8 Hz, 2H), 3.55 - 3.48 (m, 1H), 2.82 - 2.65 (m, 6H), 2.38 - 2.25 (m, 1H), 2.24 - 2.14 (m, 1H), 2.13 - 2.05 (m, 1H), 1.80 - 1.29 (m, 14H). LCMS (ESI) m/z: 571.2 $[M+H]^+$.

Example 69: (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(pyrrolidin-3-yloxy)-phenyl)sulfonyl)benzamide



(I)

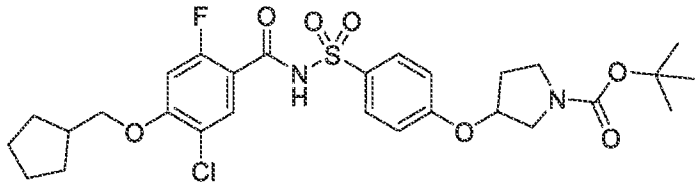
Step 1: *tert*-butyl 3-(4-sulfamoylphenoxy)pyrrolidine-1-carboxylate



[0447] To a stirred solution of *tert*-butyl 3-hydroxypyrrolidine-1-carboxylate (1.6 g, 8.56 mmol) in DMF (20 mL) was added NaH (345 mg, 8.62 mmol, 60% in mineral oil) at 0 °C. After

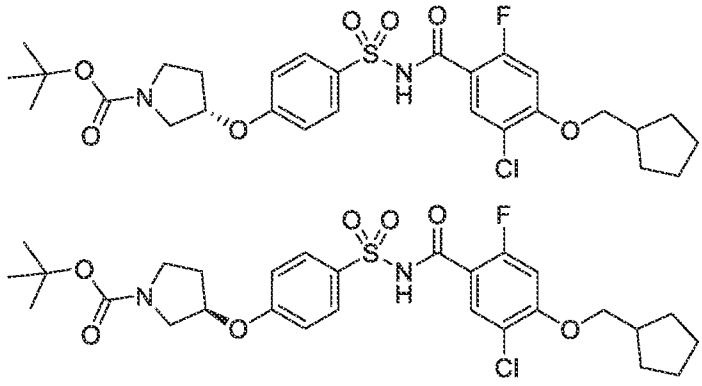
10 min, 4-fluorobenzenesulfonamide (500 mg, 2.85 mmol) was added at 0 °C and stirred for 16 h at 80 °C. After cooling to room temperature, the reaction was quenched with saturated aqueous NH_4Cl (40 mL), and extracted with EtOAc (60 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 40% EtOAc in petroleum ether) to afford the title compound (210 mg, 22%) as a white solid. LCMS (ESI) m/z: 365.0 $[M+Na]^+$.

Step 2: *tert*-butyl 3-(4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)-sulfamoyl)phenoxy)pyrrolidine-1-carboxylate



[0448] Following the procedure described in Example **59** and replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzenesulfonamide with *tert*-butyl 3-(4-sulfamoylphenoxy)pyrrolidine-1-carboxylate, the title compound was obtained as yellow oil. LCMS (ESI) m/z: 497.2 $[M-100+H]^+$.

Step 3: (*R*)-*tert*-butyl 3-(4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)-sulfamoyl)phenoxy)pyrrolidine-1-carboxylate and (*S*)-*tert*-butyl 3-(4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)-phenoxy)pyrrolidine-1-carboxylate



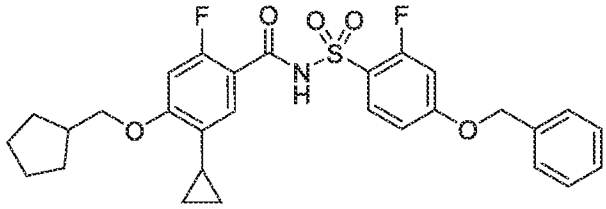
[0449] *tert*-butyl 3-(4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl) phenoxy)pyrrolidine-1-carboxylate (270 mg, 0.45 mmol) was separated by using chiral SFC (Chiralpak AD (250 mm * 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% $NH_3 \cdot H_2O$ = 50/50; 80 mL/min) to afford (*R*)-*tert*-butyl 3-(4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)phenoxy)pyrrolidine-1-carboxylate (100 mg, first peak) and (*S*)-*tert*-

butyl 3-(4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)phenoxy)pyrrolidine-1-carboxylate (100 mg, second peak). Absolute configuration was arbitrarily assigned to each enantiomer. LCMS (ESI) m/z: 619.1 $[M+Na]^+$.

Step 4: (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(pyrrolidin-3-yloxy)phenyl)sulfonyl)benzamide

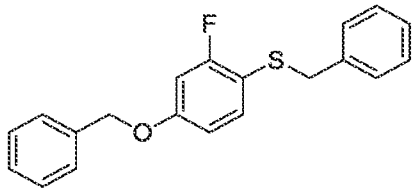
[0450] To a solution of (*R*)-*tert*-butyl 3-(4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)phenoxy)pyrrolidine-1-carboxylate (70 mg, 0.12 mmol) in DCM (1 mL) was added trifluoroacetic acid (0.07 mL, 1 mmol) at room temperature. The mixture was stirred at room temperature for 1 h. The mixture was concentrated and purified by reverse phase chromatography (acetonitrile 25 - 55% / (0.05% $NH_3 \cdot H_2O$ +10 mM NH_4HCO_3) in water) to afford the title compound (29 mg, 49%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 - 7.70 (m, 3H), 6.98 - 6.85 (m, 3H), 5.12 - 4.99 (m, 1H), 3.93 (d, J = 6.8 Hz, 2H), 3.26 - 3.20 (m, 2H), 3.19 - 3.11 (m, 2H), 2.35 - 2.25 (m, 1H), 2.23 - 2.10 (m, 1H), 2.07 - 1.95 (m, 1H), 1.81 - 1.70 (m, 2H), 1.64 - 1.48 (m, 4H), 1.40 - 1.25 (m, 2H). LCMS (ESI) m/z: 497.0 $[M+H]^+$.

Example 70: *N*-((4-(benzyloxy)-2-fluorophenyl)sulfonyl)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzamide



(I)

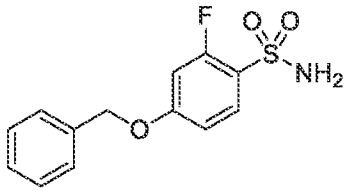
Step 1: benzyl(4-(benzyloxy)-2-fluorophenyl)sulfane



[0451] To a solution of 4-benzyloxy-1-bromo-2-fluoro-benzene (830 mg, 2.95 mmol), *tris*-(dibenzylideneacetone)dipalladium (270 mg, 0.3 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (342 mg, 0.59 mmol) and DIPEA (1.03 mL, 5.9 mmol) in 1,4-dioxane (11 mL) under nitrogen atmosphere. Phenylmethanethiol (0.52 mL, 4.43 mmol) was added and the reaction was stirred at 120 °C under nitrogen atmosphere for 16 h. After cooling to room temperature, the reaction was diluted with water (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4,

filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% EtOAc in petroleum ether) to afford the title compound (510 mg, 53%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 - 7.51 (m, 4H), 7.50 - 7.45 (m, 1H), 7.41 - 7.29 (m, 6H), 6.90 - 6.80 (m, 1H), 6.79 - 6.69 (m, 1H), 5.16 (s, 2H), 4.10 (s, 2H).

Step 2: 4-(benzyloxy)-2-fluorobenzenesulfonamide

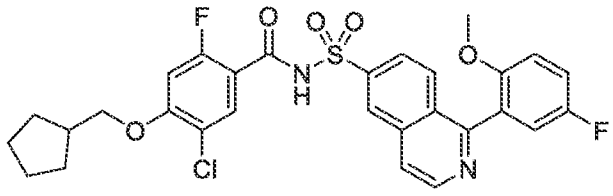


[0452] To a solution of benzyl(4-(benzyloxy)-2-fluorophenyl)sulfane (500 mg, 1.54 mmol) in acetonitrile (4 mL), acetic acid (3 mL) and water (3 mL) was added 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (911 mg, 4.62 mmol) slowly at 0 °C. After stirring at 0 °C for 1 h, NH_3•H_2O (2.7 mL, 36.8 mmol) was added at 0 °C. The reaction was stirred at 25 °C for 2 h. The reaction was diluted with water (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (150 mg, crude) as colorless oil that required no further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 - 7.72 (m, 1H), 7.39 - 7.36 (m, 6H), 6.87 - 6.73 (m, 1H), 5.15 (s, 2H).

Step 3: *N*-((4-(benzyloxy)-2-fluorophenyl)sulfonyl)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzamide

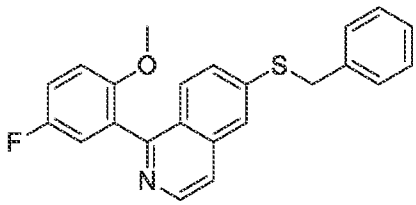
[0453] Following the procedure described in Example **63** and replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzenesulfonamide with 4-(benzyloxy)-2-fluorobenzenesulfonamide, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 7.87 (t, J = 8.4 Hz, 1H), 7.50 - 7.33 (m, 5H), 7.17 (d, J = 12.4 Hz, 1H), 7.07 (br d, J = 8.0 Hz, 2H), 6.91 (d, J = 12.8 Hz, 1H), 5.22 (s, 2H), 3.95 (d, J = 6.8 Hz, 2H), 2.40 - 2.25 (m, 1H), 2.04 - 1.92 (m, 1H), 1.85 - 1.70 (m, 2H), 1.69 - 1.45 (m, 4H), 1.41 - 1.29 (m, 2H), 0.92 - 0.82 (m, 2H), 0.73 - 0.59 (m, 2H). LCMS (ESI) m/z: 542.1[M+H]$^+$.

Example 72: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((1-(5-fluoro-2-methoxyphenyl)isoquinolin-6-yl)sulfonyl)benzamide



(I)

Step 1: 6-(benzylthio)-1-(5-fluoro-2-methoxyphenyl)isoquinoline

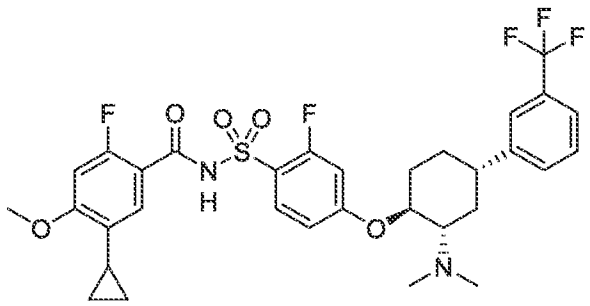


[0454] To a solution of (5-fluoro-2-methoxyphenyl)boronic acid (892 mg, 5.25 mmol) and 6-(benzylthio)-1-chloroisoquinoline (1.0 g, 3.5 mmol) in 1,4-dioxane (20 mL) and water (2 mL) was added K_3PO_4 (2.2 g, 10.5 mmol) and bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)-dichloropalladium(II) (248 mg, 0.35 mmol) at room temperature under nitrogen atmosphere. Then the mixture was stirred at 100 °C for 16 h. After cooling to room temperature, the reaction was diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to afford the title compound (1.1 g, 84%) as yellow oil. LCMS (ESI) m/z: 376.2 $[M+H]^+$.

Step 2: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((1-(5-fluoro-2-methoxyphenyl)isoquinolin-6-yl)sulfonyl)benzamide

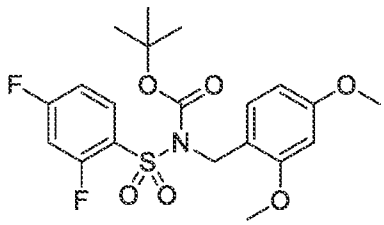
[0455] Following the procedure described in **Example 71** and making non-critical variations as required to replace *trans*-2-(4-(benzylthio)-3-fluorophenyl)-*N*,*N*-dimethylcyclohexanamine with 6-(benzylthio)-1-(5-fluoro-2-methoxyphenyl)isoquinoline, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 - 8.70 (m, 2H), 8.21 (d, J = 5.6 Hz, 1H), 8.03 - 7.99 (m, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.43 - 7.35 (m, 1H), 7.27 - 7.22 (m, 2H), 7.20 (d, J = 12.8 Hz, 1H), 4.01 (d, J = 6.8 Hz, 2H), 3.64 (s, 3H), 2.36 - 2.27 (m, 1H), 1.81 - 1.40 (m, 2H), 1.64 - 1.50 (m, 4H), 1.37 - 1.28 (m, 2H). LCMS (ESI) m/z: 587.2 $[M+H]^+$.

Example 74: 5-cyclopropyl-*N*-((4-(((*1S,2S,4S*)-2-(dimethylamino)-4-(3-(trifluoromethyl)phenyl)cyclohexyl)oxy)-2-fluorophenyl)sulfonyl)-2-fluoro-4-methoxybenzamide



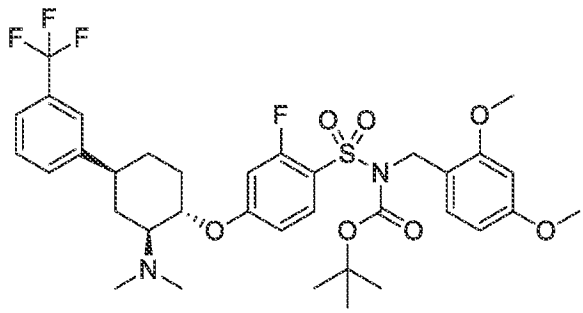
(I)

Step 1: *tert*-butyl (2,4-difluorophenyl)sulfonyl(2,4-dimethoxybenzyl)carbamate



[0456] To a stirred solution of 2,4-dimethoxybenzylamine (7.87 g, 47.04 mmol) and pyridine (19 mL, 235.18 mmol) in DCM (220 mL) was added 2,4-difluorobenzenesulfonylchloride (10.0 g, 47.04 mmol) at 0 °C. The reaction was stirred at room temperature for 1 h. Boc_2O (50.85 g, 233 mmol) and DMAP (5.69 g, 46.6 mmol) were added and the mixture was stirred at 40 °C for 16 h. After cooling to room temperature, the reaction was diluted with water (100 mL) and extracted with DCM (150 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 15% EtOAc in petroleum ether) to afford the title compound (15 g, 73%) as a yellow solid. LCMS (ESI) m/z: 466.1 $[M+Na]^+$.

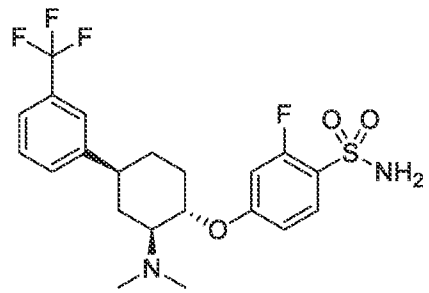
Step 2: *tert*-butyl 2,4-dimethoxybenzyl((4-(((*1S,2S,4S*)-2-(dimethylamino)-4-(3-(trifluoromethyl)phenyl)cyclohexyl)oxy)-2-fluorophenyl)sulfonyl)carbamate



[0457] To a solution of NaH (100 mg, 2.51 mmol, 60% in mineral oil) in DMF (18 mL) was added (*1S,2S,4S*)-2-(dimethylamino)-4-[3-(trifluoromethyl)phenyl]cyclo hexanol (0.6 g, 2.09 mmol) at 0 °C under nitrogen atmosphere. After stirring at 0 °C for 0.5 h, *tert*-butyl *N*-(2,4-

difluorophenyl)sulfonyl-*N*-[(2,4-dimethoxyphenyl)methyl]carbamate (1.08 g, 2.09 mmol) was added dropwise at 0 °C. The reaction was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous NH_4Cl (50 mL), extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL x 5), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether then 5% MeOH in DCM) to afford the title compound (0.60 g, 40%) as colorless oil. LCMS (ESI) m/z: 711.1 $[M+H]^+$.

Step 3: 4-(((*1S,2S,4S*)-2-(dimethylamino)-4-(3-(trifluoromethyl)phenyl)cyclohexyl)oxy)-2-fluorobenzenesulfonamide



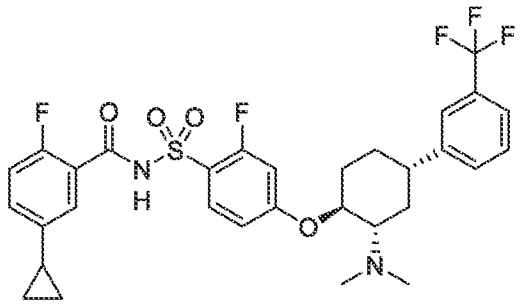
[0458] To a stirred solution of *tert*-butyl 2,4-dimethoxybenzyl((4-(((*1S,2S,4S*)-2-(dimethylamino)-4-(3-(trifluoromethyl)phenyl)cyclohexyl)oxy)-2-fluorophenyl)sulfonyl) carbamate (0.6 g, 0.84 mmol) in DCM (30 mL) was added TFA (96 mg, 0.84 mmol) and triethylsilane (1.41 mL, 8.81 mmol) at room temperature. Then the reaction was stirred at room temperature for 1 h. The mixture was concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 10% MeOH in DCM) to afford the title compound (0.32 g, 82%) as yellow oil. LCMS (ESI) m/z: 461.3 $[M+H]^+$.

Step 4: 5-cyclopropyl-*N*-((4-(((*1S,2S,4S*)-2-(dimethylamino)-4-(3-(trifluoromethyl)-phenyl)cyclohexyl)oxy)-2-fluorophenyl)sulfonyl)-2-fluoro-4-methoxybenzamide

[0459] Following the procedure described in Example **59** and making non-critical variations as required to replace 4-(((*1S,2S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzenesulfonamide and 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid with 4-(((*1S,2S,4S*)-2-(dimethylamino)-4-(3-(trifluoromethyl)phenyl)cyclohexyl)oxy)-2-fluorobenzenesulfonamide and 5-cyclopropyl-2-fluoro-4-methoxybenzoic acid, the title compound was obtained as a white solid. ^1H NMR (400 MHz, DMSO-*d*6) δ 9.31 (s, 1H), 7.76 (t, *J* = 8.8 Hz, 1H), 7.71 - 6.68 (m, 1H), 7.65 - 7.54 (m, 3H), 7.23 (d, *J* = 8.4 Hz, 1H), 6.97 - 6.86 (m, 2H), 6.69 (d, *J* = 12.8 Hz, 1H), 4.91 - 4.79 (m, 1H), 3.81 (s, 3H), 3.77 - 3.58 (m, 1H), 2.96 - 2.89 (m, 1H), 2.85 - 2.60 (m, 6H), 2.36 - 2.28 (m, 1H), 2.25 - 2.15 (m, 1H), 2.01 - 1.94 (m, 1H), 1.90 -

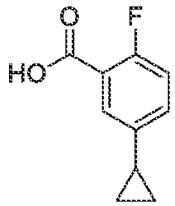
1.75 (m, 3H), 1.57 - 1.45 (m, 1H), 0.90 - 0.81 (m, 2H), 0.55 - 0.47(m, 2H). LCMS (ESI) m/z: 653.3 $[M+H]^+$.

Example 75: 5-cyclopropyl-*N*-((4-(((*1S,2S,4S*)-2-(dimethylamino)-4-(3-(trifluoromethyl)-phenyl)cyclohexyl)oxy)-2-fluorophenyl)sulfonyl)-2-fluorobenzamide



(I)

Step 1: 5-cyclopropyl-2-fluorobenzoic acid

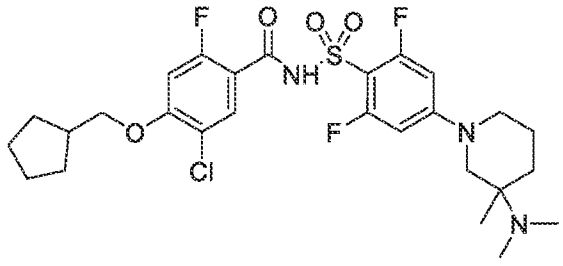


[0460] To a solution of methyl 5-cyclopropyl-2-fluorobenzoate (580 mg, 2.99 mmol) in water (7.5 mL) and THF (7.5 mL) was added LiOH (716 mg, 30 mmol) at room temperature and the reaction was stirred at room temperature for 16 h. The reaction was quenched with aqueous HCl (1 M) to pH = 2, and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (420 mg, 71%) as a white solid. LCMS (ESI) m/z: 181.1 $[M+H]^+$.

Step 2: 5-cyclopropyl-*N*-((4-(((*1S,2S,4S*)-2-(dimethylamino)-4-(3-(trifluoromethyl)phenyl)cyclohexyl)oxy)-2-fluorophenyl)sulfonyl)-2-fluorobenzamide

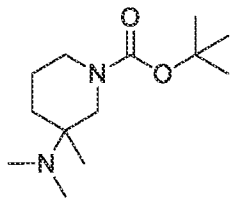
[0461] Following the procedure described in Example 74 and making non-critical variations as required to replace 5-cyclopropyl-2-fluoro-4-methoxybenzoic acid with 5-cyclopropyl-2-fluorobenzoic acid, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 - 7.72 (m, 1H), 7.69 - 7.55 (m, 4H), 7.39 - 7.30 (m, 1H), 7.06 - 6.97 (m, 1H), 6.96 - 6.86 (m, 3H), 4.85 - 4.75 (m, 1H), 3.83 - 3.76 (m, 1H), 2.95 - 2.87 (m, 1H), 2.63 (s, 6H), 2.33 - 2.25 (m, 1H), 2.20 - 2.05 (m, 1H), 1.93 - 1.61 (m, 3H), 1.57 - 1.42 (m, 1H), 1.23 - 1.16 (m, 1H), 0.96 - 0.86 (m, 2H), 0.62 - 0.53 (m, 2H). LCMS (ESI) m/z: 623.3 $[M+H]^+$.

Example 76: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-(3-(dimethylamino)-3-methylpiperidin-1-yl)-2,6-difluorophenyl)sulfonyl)-2-fluorobenzamide



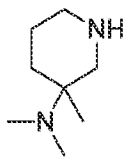
(I)

Step 1: tert-butyl 3-(dimethylamino)-3-methylpiperidine-1-carboxylate



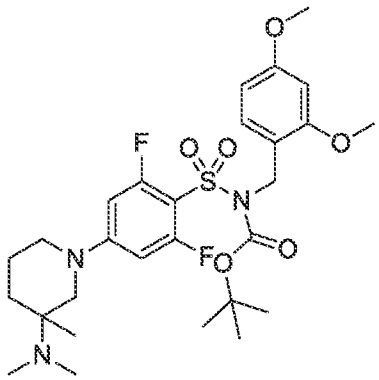
[0462] To a mixture of *tert*-butyl 3-amino-3-methylpiperidine-1-carboxylate (0.4 g, 1.87 mmol) in MeCN (20 mL) was added formaldehyde (16.22 mL, 215.78 mmol, 2 M in THF) and $NaBH_3CN$ (0.59 g, 9.33 mmol). The mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (15 mL) to pH > 7, and extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (425 mg, 94%) as yellow oil that required no further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 3.66 - 3.35 (m, 2H), 3.26 - 3.02 (m, 2H), 2.25 (s, 6H), 1.72 - 1.47 (m, 4H), 1.46 (s, 9H), 0.88 (s, 3H).

Step 2: *N,N*,3-trimethylpiperidin-3-amine



[0463] To a stirred solution of *tert*-butyl 3-(dimethylamino)-3-methyl-piperidine-1-carboxylate (0.4 g, 1.65 mmol) in DCM (8 mL) was added TFA (3 mL). The reaction was stirred at room temperature for 16 h. The reaction was concentrated in vacuo to remove most solvent and diluted with water (20 mL), neutralized with 10% aqueous NaOH solution (pH > 7) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (220 mg, crude) as yellow oil that required no further purification.

Step 3: *tert*-butyl 2,4-dimethoxybenzyl((4-(3-(dimethylamino)-3-methylpiperidin-1-yl)-2,6-difluorophenyl)sulfonyl)carbamate

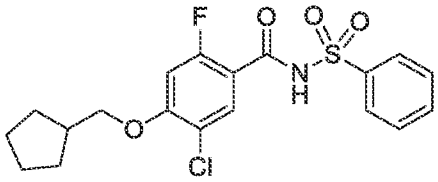


[0464] Following the procedure described in Example **62** and making non-critical variations as required to replace *N,N*-dimethylpiperidin-3-amine with *N,N,3*-trimethylpiperidin-3-amine and replace 2,4,6-trifluorobenzenesulfonamide with *tert*-butyl 2,4-dimethoxybenzyl((2,4,6-trifluorophenyl)sulfonyl)carbamate, the title compound was obtained as colorless oil. LCMS (ESI) m/z: 584.3 $[M+H]^+$.

Step 4: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-(3-(dimethylamino)-3-methylpiperidin-1-yl)-2,6-difluorophenyl)sulfonyl)-2-fluorobenzamide

[0465] Following the procedure described in Example **74** and making non-critical variations as required to replace *tert*-butyl 2,4-dimethoxybenzyl((4-(((*1S,2S,4S*)-2-(dimethylamino)-4-(3-(trifluoromethyl)phenyl)cyclohexyl)oxy)-2-fluorophenyl)sulfonyl)carbamate with *tert*-butyl 2,4-dimethoxybenzyl((4-(3-(dimethylamino)-3-methylpiperidin-1-yl)-2,6-difluorophenyl)sulfonyl)carbamate and replace 5-cyclopropyl-2-fluoro-4-methoxybenzoic acid with 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.74 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 12.4 Hz, 1H), 6.60 (d, *J* = 12.4 Hz, 2H), 3.95 (d, *J* = 6.8 Hz, 2H), 3.47 - 3.35 (m, 2H), 3.30 - 3.15 (m, 2H), 2.57 (s, 6H), 2.36 - 2.29 (m, 1H), 1.80 - 1.69 (m, 5H), 1.63 - 1.51 (m, 5H), 1.39 - 1.32 (m, 2H), 1.12 (s, 3H). LCMS (ESI) m/z: 588.2 $[M+H]^+$.

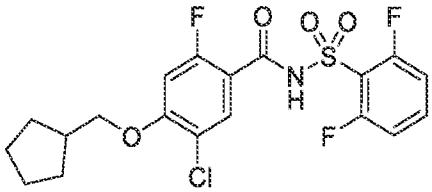
Example 78: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(phenylsulfonyl)benzamide



(I)

[0466] Following the procedure described in Example **59** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzene-sulfonamide with benzenesulfonamide, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H), 7.98 (d, J = 7.2 Hz, 2H), 7.77 - 7.70 (m, 1 H) 7.70 - 7.63 (m, 3H), 7.21 (d, J = 12.8 Hz, 1H), 4.01 (d, J = 6.8 Hz, 2H), 2.37 - 2.28 (m, 1H), 1.81 - 1.70 (m, 2H), 1.65 - 1.47 (m, 4H), 1.39 - 1.28 (m, 2H). LCMS (ESI) m/z: 412.2 $[M+H]^+$.

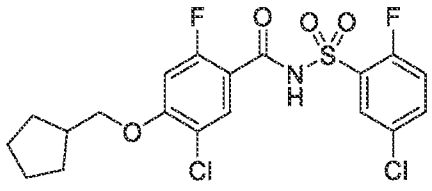
Example 79: 5-chloro-4-(cyclopentylmethoxy)-*N*-((2,6-difluorophenyl)sulfonyl)-2-fluorobenzamide



(I)

[0467] Following the procedure described in Example **59** and replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzenesulfonamide with 2,6-difluorobenzenesulfonamide, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 - 7.75 (m, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.33 (t, J = 9.2 Hz, 2H), 7.22 (d, J = 12.4 Hz, 1H), 4.02 (d, J = 6.8 Hz, 2H), 2.38 - 2.26 (m, 1H), 1.83 - 1.70 (m, 2H), 1.68 - 1.48 (m, 4H), 1.40 - 1.29 (m, 2H). LCMS (ESI) m/z: 447.9 $[M+H]^+$.

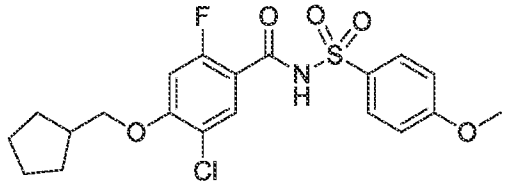
Example 80: 5-chloro-*N*-((5-chloro-2-fluorophenyl)sulfonyl)-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

[0468] Following the procedure described in Example **1** and making non-critical variations as required to replace 5-chloro-2,4-difluorobenzene-1-sulfonyl chloride and 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-chloro-2-fluorobenzene-1-sulfonyl chloride and 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 - 7.87 (m, 1H), 7.86 - 7.81 (m, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.58 - 7.49 (m, 1H), 7.19 (d, J = 12.4 Hz, 1H), 4.01 (d, J = 7.2 Hz, 2H), 2.38 - 2.28 (m, 1H), 1.80 - 1.71 (m, 2H), 1.65 - 1.51 (m, 4H), 1.38 - 1.31 (m, 2H). LCMS (ESI) m/z: 464.1 $[M+H]^+$.

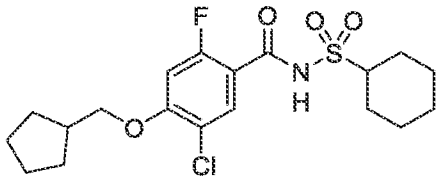
Example 81: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-methoxyphenyl)sulfonyl)-benzamide



(I)

[0469] Following the procedure described in Example **59** and replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzenesulfonamide with 4-methoxy-benzenesulfonamide, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H), 7.92 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 12.4 Hz, 1H), 7.16 (d, J = 8.8 Hz, 2H), 4.01 (d, J = 6.8 Hz, 2H), 3.86 (s, 3H), 2.37 - 2.25 (m, 1H), 1.82 - 1.70 (m, 2H), 1.66 - 1.47 (m, 4H), 1.39 - 1.27 (m, 2H), LCMS (ESI) m/z: 442.0 $[M+H]^+$.

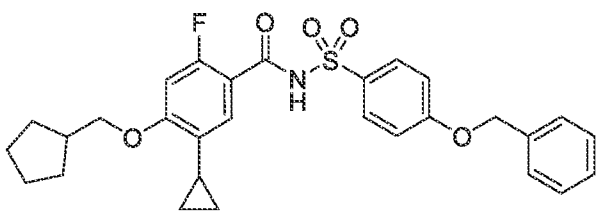
Example 82: 5-chloro-*N*-(cyclohexylsulfonyl)-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

[0470] Following the procedure described in Example **80** and making non-critical variations as required to replace 5-chloro-2-fluorobenzene-1-sulfonyl chloride with cyclohexanesulfonyl chloride, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 12.4 Hz, 1H), 4.03 (d, J = 6.8 Hz, 2H), 3.55 - 3.45 (m, 1H), 2.39 - 2.28 (m, 1H), 2.09 - 2.01 (m, 2H), 1.88 - 1.71 (m, 4H), 1.68 - 1.59 (m, 3H), 1.58 - 1.51 (m, 2H), 1.50 - 1.41 (m, 2H), 1.40 - 1.23 (m, 4H), 1.22 - 1.09 (m, 1H). LCMS (ESI) m/z: 418.1 $[M+H]^+$.

Example 83: *N*-((4-(benzyloxy)phenyl)sulfonyl)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzamide

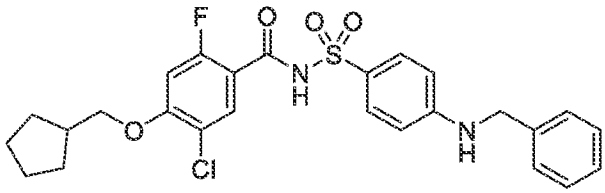


(I)

[0471] Following the procedure described in Example **69** and making non-critical variations as required to replace *tert*-butyl 3-hydroxypyrrolidine-1-carboxylate and 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid with phenylmethanol and 4-(cyclopentylmethoxy)-5-

cyclopropyl-2-fluorobenzoic acid, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (s, 1H), 7.91 (d, J = 8.8 Hz, 2H), 7.49 - 7.33 (m, 5H), 7.23 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 13.2 Hz, 1H), 5.21 (s, 2H), 3.94 (d, J = 6.8 Hz, 2H), 2.37 - 2.25 (m, 1H), 2.01 - 1.93 (m, 1H), 1.85 - 1.70 (m, 2H), 1.65 - 1.48 (m, 4H), 1.41 - 1.30 (m, 2H), 0.89 - 0.81 (m, 2H), 0.68 - 0.60 (m, 2H). LCMS (ESI) m/z: 524.2 $[M+H]^+$.

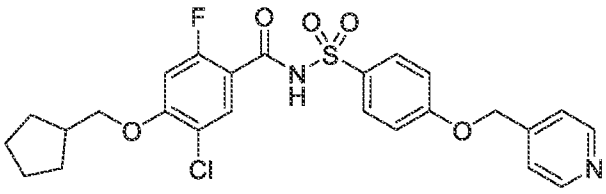
Example 84: *N*-((4-(benzylamino)phenyl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

[0472] Following the procedure described in Example **59** and making non-critical variations as required to replace 4-(((*1S,2S*)-2-(dimethylamino) cyclohexyl) amino)-2-fluorobenzene-sulfonamide with 4-(benzylamino)benzenesulfonamide (Reference: *Bioorg. Med. Chem. Lett.*, **2014**, 24, 1776), the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 7.67 - 7.59 (m, 3H), 7.36 - 7.33 (m, 4H), 7.27 - 7.22 (m, 1H), 7.19 (d, J = 11.6 Hz, 1H), 6.68 (d, J = 8.8 Hz, 2H), 4.35 (d, J = 5.6 Hz, 2H), 4.00 (d, J = 6.8 Hz, 2H), 2.37 - 2.27 (m, 1H), 1.83 - 1.70 (m, 2H), 1.65 - 1.49 (m, 4H), 1.48 - 1.27 (m, 2H). LCMS (ESI) m/z: 517.1 $[M+H]^+$.

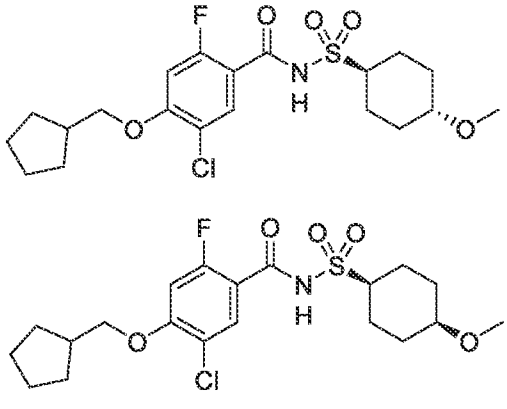
Example 85: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(pyridin-4-ylmethoxy)-phenyl)sulfonyl)benzamide



(I)

[0473] Following the procedure described in Example **83** and making non-critical variations as required to replace phenylmethanol and 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid with pyridin-4-yl methanol and 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (d, J = 5.6 Hz, 2H), 7.92 (d, J = 9.2 Hz, 2H), 7.67 (d, J = 7.2 Hz, 1H), 7.46 (d, J = 5.6 Hz, 2H), 7.23 (d, J = 9.2 Hz, 2H), 7.19 (d, J = 12.4 Hz, 1H), 5.30 (s, 2H), 4.00 (d, J = 6.8 Hz, 2H), 2.37 - 2.25 (m, 1H), 1.80 - 1.71 (m, 2H), 1.65 - 1.46 (m, 4H), 1.37 - 1.25 (m, 2H). LCMS (ESI) m/z: 519.2 $[M+H]^+$.

Example 86 and Example 87: *trans*-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-methoxycyclohexyl)sulfonyl)benzamide, and *cis*-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-methoxycyclohexyl)sulfonyl)benzamide

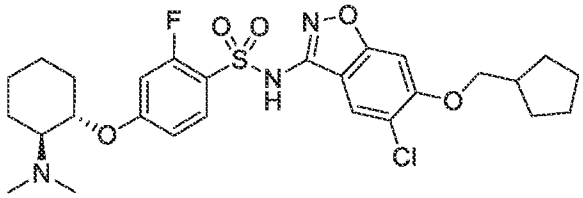


(I)

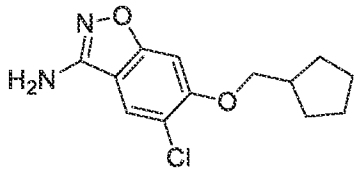
[0474] (These compounds may also be referred to as 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(((1r,4r)-4-methoxycyclohexyl)sulfonyl)benzamide, and 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(((1s,4s)-4-methoxycyclohexyl)sulfonyl)benzamide.

[0475] To a solution of NaH (28.21 mg, 0.71 mmol, 60% in mineral oil) in THF (4 mL) was added 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-benzamide (113 mg, 0.42 mmol) at 0 oC and the reaction was stirred at 0 oC for 0.5 h. 4-methoxycyclohexanesulfonyl chloride (100 mg, 0.47 mmol) was added and the reaction was stirred at room temperature for 3 h. The reaction was then quenched with saturated aqueous NH4Cl solution (30 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na2SO4, filtered and concentrated in vacuo. The crude residue was purified by reverse phase chromatography (acetonitrile 65 - 95% / 0.2% HCOOH in water) to afford cis-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-methoxycyclohexyl) sulfonyl)benzamide (10 mg, first peak) and trans-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-methoxycyclohexyl)sulfonyl)-benzamide (10 mg, second peak) both as a white solid. **Example 86**: trans ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (s, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 12.4 Hz, 1H), 4.03 (d, J = 6.8 Hz, 2H), 3.53 - 3.43 (m, 1H), 3.23 (s, 3H), 3.17 - 3.07 (m, 1H), 2.40 - 2.27 (m, 1H), 2.15 - 2.03 (m, 4H), 1.83 - 1.73 (m, 2H), 1.65 - 1.50 (m, 6H), 1.39 - 1.29 (m, 2H), 1.26 - 1.14 (m, 2H). LCMS (ESI) m/z: 448.2 $[M+H]^+$. **Example 87**: cis ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.07 (m, J = 8.0 Hz, 1H), 6.70 (d, J = 13.6 Hz, 1H), 3.96 (d, J = 6.8 Hz, 2H), 3.78 - 3.68 (m, 1H), 3.50 - 3.45 (m, 1H), 3.30 (s, 3H), 2.51 - 2.40 (m, 1H), 2.17 - 2.08 (m, 2H), 2.05 - 1.95 (m, 2H), 1.93 - 1.84 (m, 2H), 1.73 - 1.59 (m, 6H), 1.49 - 1.37 (m, 4H). LCMS (ESI) m/z: 448.2 $[M+H]^+$.

Example 88: *N*-(5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-yl)-4-(((*1S,2S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzenesulfonamide

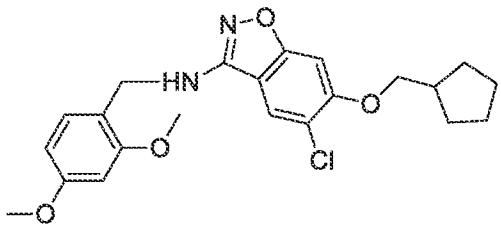


Step 1: 5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-amine



[0476] To a solution of 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzonitrile (2 g, 7.88 mmol) in DMF (40 mL) was added *t*-BuOK (2.65 g, 23.65 mmol) at room temperature under nitrogen atmosphere. The reaction was stirred at room temperature for 30 min. Then *N*-hydroxyacetamide (1.8 g, 23.65 mmol) was added and then the reaction was stirred at 50 °C for 16 h. The reaction was diluted with water (80 mL) and extracted with EtOAc (150 mL x 3). The combined organic lawyers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 20% EtOAc in petroleum ether) to afford the title compound (820 mg, 39%) as a white solid. LCMS (ESI) m/z: 267.1 $[M+H]^+$.

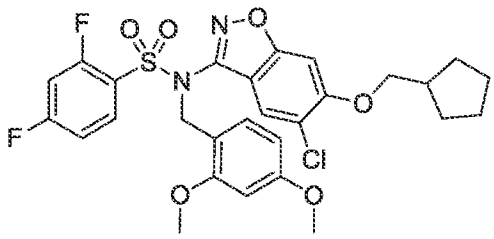
Step 2: 5-chloro-6-(cyclopentylmethoxy)-*N*-(2,4-dimethoxybenzyl)benzo[*d*]isoxazol-3-amine



[0477] To a stirred solution of 5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-amine (0.71 g, 2.65 mmol) and 2,4-dimethoxybenzaldehyde (0.4 g, 2.41 mmol) in DCM (12 mL) was added $TiCl(O\textit{i}\text{-}Pr)_3$ (1.86 mL, 5.54 mmol) in one portion under nitrogen atmosphere. The solution was stirred for 10 min before the portion wise addition of $NaBH(OAc)_3$ (1.53 g, 7.22 mmol) at 0 °C. The reaction was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (50 mL), extracted with DCM (50 mL x 3). The combined organic lawyers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and

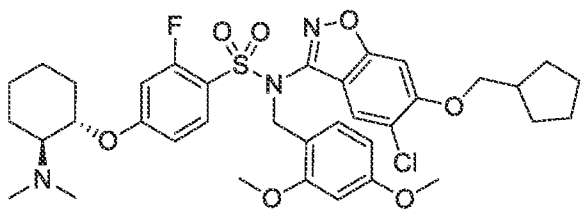
concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 25% EtOAc in petroleum ether) to afford the title compound (0.53 g, 53%) as a white solid. LCMS (ESI) m/z: 417.2 $[M+H]^+$.

Step 3: *N*-(5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-yl)-*N*-(2,4-dimethoxybenzyl)-2,4-difluorobenzenesulfonamide



[0478] To a solution of 5-chloro-6-(cyclopentylmethoxy)-*N*-(2,4-dimethoxybenzyl)-benzo[*d*]isoxazol-3-amine (170 mg, 0.52 mmol) in THF (2 mL) was added LiHMDS (0.62 mL, 0.62 mmol, 1 M) at -78 °C. The reaction was stirred for 30 min at 0 °C and a solution of 2,4-difluorobenzenesulfonylchloride (0.22 g, 1.03 mmol) in THF (2 mL) was added dropwise at -78 °C. After the addition was complete, the cooling bath was removed. The reaction mixture was stirred at room temperature for 3 h. The reaction was diluted with water (30 mL) and extracted with EtOAc (50 mL x 3). The combined organic lawyers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to afford the title compound (160 mg, 52%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 - 7.78 (m, 1H), 7.62 (s, 1H), 7.25 - 7.14 (m, 1H), 7.12 - 6.84 (m, 3H), 6.44 - 6.27 (m, 2H), 5.00 (s, 2H), 3.92 (d, *J* = 6.8 Hz, 2H), 3.75 (s, 3H), 3.58 (s, 3H), 2.56 - 2.35 (m, 1H), 1.97 - 1.84 (m, 2H), 1.74 - 1.55 (m, 4H), 1.49 - 1.37 (m, 2H).

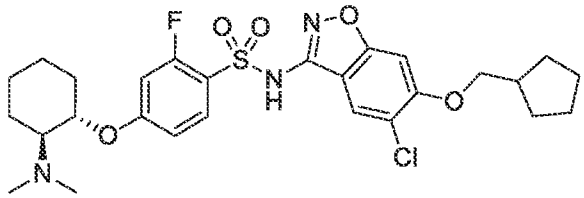
Step 4: *N*-(5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-yl)-*N*-(2,4-dimethoxybenzyl)-4-(((*1S,2S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzenesulfonamide



[0479] To a stirred solution of NaH (9 mg, 0.2 mmol, 60% in mineral oil) in DMF (1.5 mL) was added (*1S,2S*)-2-(dimethylamino)cyclohexanol (30 mg, 0.2 mmol) at 0 °C. After stirring at 0 °C for 0.5 h, *N*-(5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-yl)-*N*-(2,4-

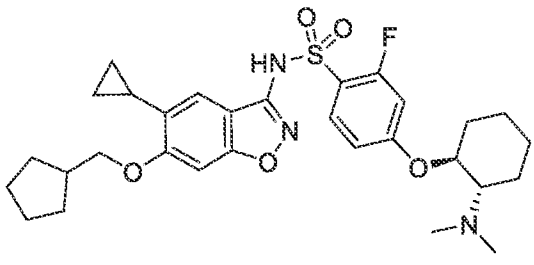
dimethoxybenzyl)-2,4-difluorobenzenesulfonamide (60 mg, 0.1 mmol) was added and the mixture was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL), extracted with EtOAc (20 mL x 3). The combined organic lawyers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (70 mg, crude) as yellow oil that required no further purification. LCMS (ESI) m/z: 716.3 $[M+H]^+$.

Step 5: *N*-(5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-yl)-4-(((*1S,2S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzenesulfonamide



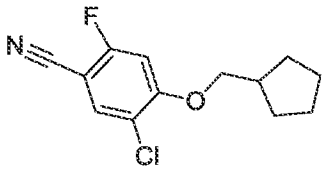
[0480] A solution of *N*-(5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-yl)-*N*-(2,4-dimethoxybenzyl)-4-(((*1S,2S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzenesulfonamide (60 mg, 0.08 mmol) in HCOOH (3 mL) was stirred at room temperature for 16 h. The mixture was concentrated in vacuo and the crude residue was purified by reverse phase chromatography (acetonitrile 35 - 65% / 0.2% HCOOH in water) to afford the title compound (2 mg, 4%) as a white solid. ^1H NMR (400 MHz, DMSO-*d6*) δ 7.74 (t, *J* = 8.4 Hz, 1H), 7.58 (s, 1H), 7.10 (s, 1H), 6.91 - 6.81 (m, 2H), 4.69 - 4.56 (m, 1H), 3.95 (d, *J* = 6.8 Hz, 2H), 3.35 - 3.25 (m, 1H), 2.67 (s, 6H), 2.57 - 2.38 (m, 1H), 2.18 - 2.10 (m, 1H), 2.05 - 1.95 (m, 1H), 1.82 - 1.73 (m, 2H), 1.69 - 1.47 (m, 6H), 1.45 - 1.24 (m, 6H). LCMS (ESI) m/z: 566.3 $[M+H]^+$.

Example 89: *N*-(6-(cyclopentylmethoxy)-5-cyclopropylbenzo[d]isoxazol-3-yl)-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzenesulfonamide



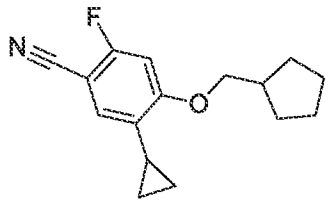
(II), (III)

Step 1: 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzonitrile



[0481] To a stirred solution of NaH (183 mg, 25 mmol, 60% in mineral oil) in DMF (20 mL) was added cyclopentylmethanol (500 mg, 2.85 mmol) at 0 °C. After 10 min, 5-chloro-2,4-difluorobenzonitrilee (0.72 g, 4.16 mmol) was added at 0 °C and stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous NH_4Cl (30 mL), and extracted with EtOAc (30 mL x 6). The combined organic layers were washed with brine (50 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 2% EtOAc in petroleum ether) to afford the title compound (810 mg, 77%) as a white solid. LCMS (ESI) m/z: 254.1 $[M+H]^+$.

Step 2: 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzonitrile

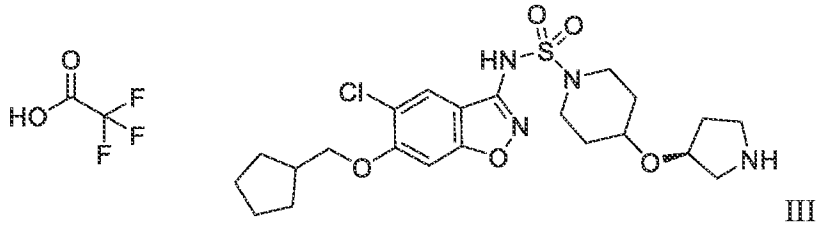


[0482] Following the procedure described in Example **4** and making non-critical variations as required to replace *tert*-butyl 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoate with 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzonitrile, the title compound was obtained as a white solid. LCMS (ESI) m/z: 260.2 $[M+H]^+$.

Step 3: *N*-(6-(cyclopentylmethoxy)-5-cyclopropylbenzo[*d*]isoxazol-3-yl)-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzenesulfonamide

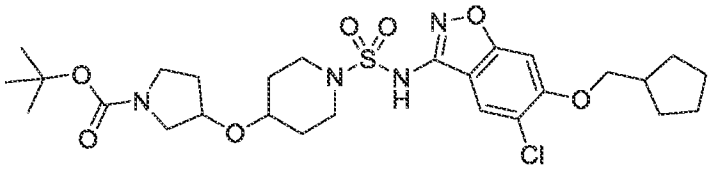
[0483] Following the procedure described in Example **88** and making non-critical variations as required to replace 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzonitrile with 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzonitrile, the title compound was obtained as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.74 (t, J = 8.8 Hz, 1H), 7.03 (s, 1H), 6.90 (d, J = 12.4 Hz, 1H), 6.87 (s, 1H), 6.86 - 6.82 (m, 1H), 4.71 - 4.58 (m, 1H), 3.90 (d, J = 6.8 Hz, 2H), 3.25 - 3.30 (m, 1H), 2.62 (s, 6H), 2.40 - 2.30 (m, 1H), 2.18 - 2.10 (m, 1H), 2.08 - 1.97 (m, 2H), 1.84 - 1.72 (m, 2H), 1.70 - 1.49 (m, 6H), 1.46 - 1.21 (m, 6H), 0.90 - 0.84 (m, 2H), 0.58 - 0.52 (m, 2H). LCMS (ESI) m/z: 572.2 $[M+H]^+$.

Example 90: (*R*)-*N*-(5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-yl)-4-(pyrrolidin-3-yloxy)piperidine-1-sulfonamide 2,2,2-trifluoroacetate



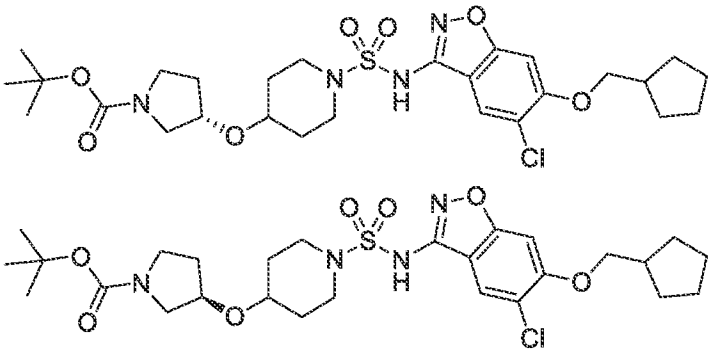
III

Step 1: *tert*-butyl 3-((1-(*N*-(5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-yl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate



[0484] To a solution of imidazole (191 mg, 2.81 mmol) and 5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-amine (150 mg, 0.56 mmol) in DCM (6 mL) was added sulfurylchloride (0.07 mL, 0.84 mmol) at -78 °C. The mixture was stirred at -78 °C for 0.5 h. Then *tert*-butyl 3-(piperidin-4-yloxy)pyrrolidine-1-carboxylate (456 mg, 1.69 mmol) in DCM (6 mL) was added dropwise. Then, the reaction was heated to 60 °C for 6 h. After cooling to room temperature, the reaction was diluted with water (20 mL) and extracted with DCM (30 mL x 3). The combined organic layers were washed with saturated aqueous citric acid (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 5% MeOH in DCM) to afford the title compound (120 mg, 36%) as colorless oil. LCMS (ESI) m/z: 499.2 $[M-100+H]^+$.

Step 2: (*S*)-*tert*-butyl 3-((1-(*N*-(5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-yl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate and (*R*)-*tert*-butyl 3-((1-(*N*-(5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-yl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate

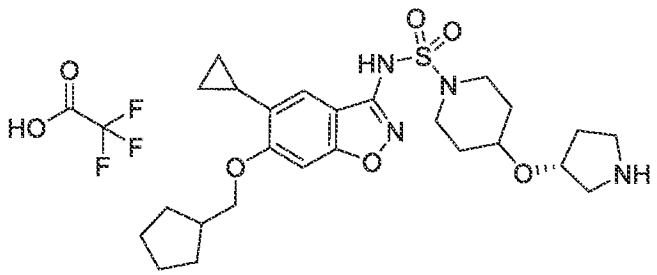


[0485] *tert*-butyl 3-((1-(*N*-(5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-yl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate (120 mg, 0.2 mmol) was separated by using chiral SFC (Chiralpak AD 250 × 30 mm I.D., 5 um; Supercritical CO_2/EtOH+0.1% $NH_3 \cdot H_2O$ = 60/40; 70 mL/min) to afford ((*S*)-*tert*-butyl 3-((1-(*N*-(5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-yl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate (43 mg, first peak) and (*R*)-*tert*-butyl 3-((1-(*N*-(5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-yl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate (42 mg, second peak) both as a white solid. Absolute configuration was arbitrarily assigned to each enantiomer. LCMS (ESI) m/z: 499.2 $[M-100+H]^+$.

Step 3: (*R*)-*N*-(5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-yl)-4-(pyrrolidin-3-yloxy)piperidine-1-sulfonamide 2,2,2-trifluoroacetate

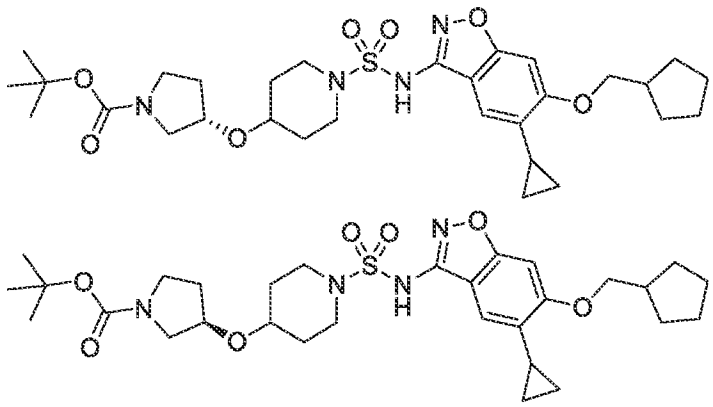
[0486] Following the procedure described in Example **1** and making non-critical variations as required to replace *tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)azetidine-1-carboxylate with (*R*)-*tert*-butyl 3-((1-(*N*-(5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-yl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.26 (s, 1H), 4.35 - 4.28 (m, 1H), 3.99 (d, J = 6.8 Hz, 2H), 3.52 - 3.40 (m, 5H), 3.25 - 3.10 (m, 2H), 2.89 (t, J = 10.4 Hz, 2H), 2.40 - 2.30 (m, 1H), 1.98 - 1.90 (m, 2H), 1.86 - 1.76 (m, 4H), 1.68 - 1.51 (m, 4H), 1.46 - 1.33 (m, 4H), LCMS (ESI) m/z: 499.1 $[M+H]^+$.

Example 91: (*S*)-*N*-(6-(cyclopentylmethoxy)-5-cyclopropylbenzo[*d*]isoxazol-3-yl)-4-(pyrrolidin-3-yloxy)piperidine-1-sulfonamide 2,2,2-trifluoroacetate



III

Step 1: (*S*)-*tert*-butyl 3-((1-(*N*-(6-(cyclopentylmethoxy)-5-cyclopropylbenzo[*d*]isoxazol-3-yl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate and (*R*)-*tert*-butyl 3-((1-(*N*-(6-(cyclopentylmethoxy)-5-cyclopropylbenzo[*d*]isoxazol-3-yl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate

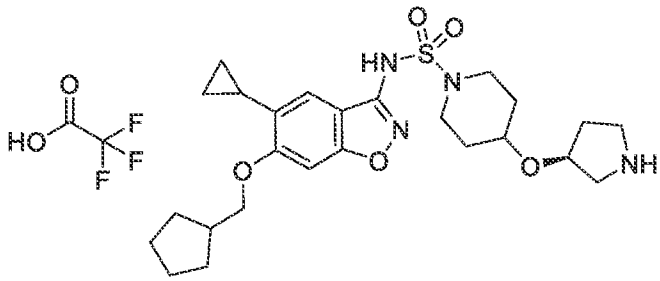


[0487] Following the procedure described in Example **90** and making non-critical variations as required to replace 5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-amine with 6-(cyclopentylmethoxy)-5-cyclopropylbenzo[*d*]isoxazol-3-amine, *tert*-butyl 3-((1-(*N*-(6-(cyclopentylmethoxy)-5-cyclopropylbenzo[*d*]isoxazol-3-yl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate was obtained as colorless oil. *tert*-butyl 3-((1-(*N*-(6-(cyclopentylmethoxy)-5-cyclopropylbenzo[*d*]isoxazol-3-yl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate (175 mg, 0.3 mmol) was separated by using chiral SFC (DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 um); Supercritical CO_2/MeOH+0.1% $NH_3 \cdot H_2O$ = 55/45; 70 mL/min) to afford (*S*)-*tert*-butyl 3-((1-(*N*-(6-(cyclopentylmethoxy)-5-cyclopropylbenzo[*d*]isoxazol-3-yl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate (70 mg, first peak) and (*R*)-*tert*-butyl 3-((1-(*N*-(6-(cyclopentylmethoxy)-5-cyclopropylbenzo[*d*]isoxazol-3-yl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate (72 mg, second peak) both as colorless oil. Absolute configuration was arbitrarily assigned to each enantiomer. LCMS (ESI) m/z: 505.2 $[M-100+H]^+$.

Step 2: (*S*)-*N*-(6-(cyclopentylmethoxy)-5-cyclopropylbenzo[*d*]isoxazol-3-yl)-4-(pyrrolidin-3-yloxy)piperidine-1-sulfonamide 2,2,2-trifluoroacetate

[0488] Following the procedure described in Example **1** and making non-critical variations as required to replace *tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)-sulfamoyl)piperidin-4-yl)oxy)azetidine-1-carboxylate with (*S*)-*tert*-butyl 3-((1-(*N*-(6-(cyclopentylmethoxy)-5-cyclopropylbenzo[*d*]isoxazol-3-yl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 - 8.42 (m, 1H), 7.41 (s, 1H), 7.05 (s, 1H), 4.35 - 4.25 (m, 1H), 3.95 (d, *J* = 6.8 Hz, 2H), 3.47 - 3.16 (m, 5H), 3.16 - 3.13 (m, 2H), 3.00 - 2.90 (m, 2H), 2.43 - 2.33 (m, 1H), 2.10 - 2.03 (m, 1H), 1.97 - 1.89 (m, 2H), 1.86 - 1.76 (m, 4H), 1.69 - 1.51 (m, 4H), 1.47 - 1.35 (m, 4 H), 0.94 - 0.86 (m, 2H), 0.59 - 0.51 (m, 2H). LCMS (ESI) m/z: 505.3 $[M+H]^+$.

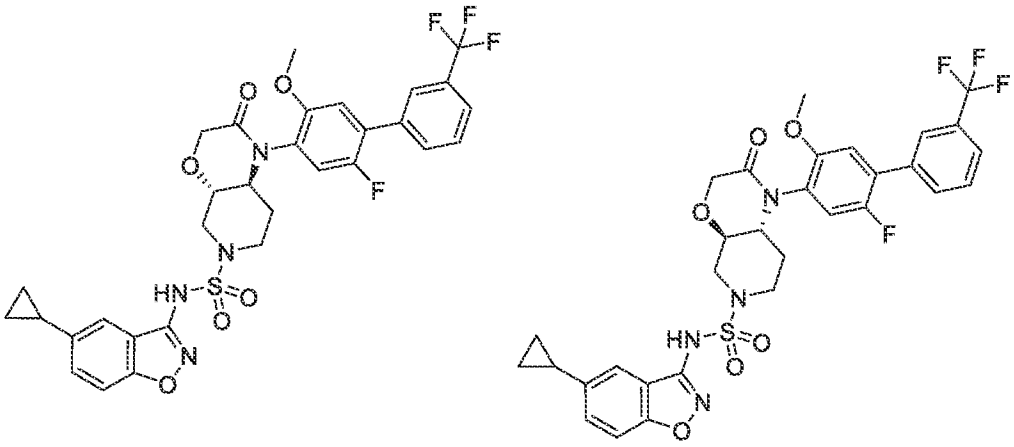
Example 92: (*R*)-*N*-(6-(cyclopentylmethoxy)-5-cyclopropylbenzo[*d*]isoxazol-3-yl)-4-(pyrrolidin-3-yloxy)piperidine-1-sulfonamide 2,2,2-trifluoroacetate



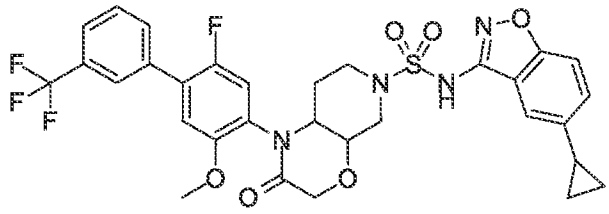
(III)

[0489] Following the procedure described in Example **91** and making non-critical variations as required to replace (*S*)-*tert*-butyl 3-((1-(*N*-(6-(cyclopentylmethoxy)-5-cyclopropylbenzo[*d*]isoxazol-3-yl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate with (*R*)-*tert*-butyl 3-((1-(*N*-(6-(cyclopentylmethoxy)-5-cyclopropylbenzo[*d*]isoxazol-3-yl)sulfamoyl)piperidin-4-yl)oxy)pyrrolidine-1-carboxylate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 - 8.44 (m, 1H), 7.37 (s, 1H), 7.01 (s, 1H), 4.34 - 4.27 (m, 1H), 3.94 (d, J = 6.8 Hz, 2H), 3.50 - 3.14 (m, 5H), 3.16 - 3.14 (m, 2H), 2.97 - 2.86 (m, 2H), 2.43 - 2.31 (m, 1H), 2.10 - 2.01 (m, 1H), 1.96 - 1.89 (m, 2H), 1.86 - 1.76 (m, 4H), 1.67 - 1.50 (m, 4H), 1.45 - 1.34 (m, 4H), 0.92 - 0.86 (m, 2H), 0.58 - 0.51 (m, 2H). LCMS (ESI) m/z: 505.2 $[M+H]^+$.

Example 93 and Example 94: (4a*R*,8a*R*)-*N*-(5-cyclopropylbenzo[*d*]isoxazol-3-yl)-1-(2-fluoro-5-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-2-oxohexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazine-6(7*H*)-sulfonamide, and (4a*S*,8a*S*)-*N*-(5-cyclopropylbenzo[*d*]isoxazol-3-yl)-1-(2-fluoro-5-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-2-oxohexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazine-6(7*H*)-sulfonamide



Step 1: *trans*-*N*-(5-cyclopropylbenzo[*d*]isoxazol-3-yl)-1-(2-fluoro-5-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-2-oxohexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazine-6(7*H*)-sulfonamide

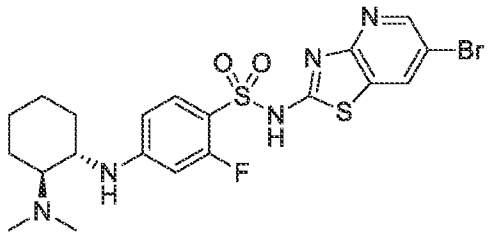


[0490] Following the procedure described in Example **90** and making non-critical variations as required to replace *tert*-butyl 3-(piperidin-4-yloxy)pyrrolidine-1-carboxylate and 5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-amine with *trans*-1-(2-fluoro-5-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)hexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazin-2(3*H*)-one (Reference: WO2019/191702) and 5-cyclopropylbenzo[*d*]isoxazol-3-amine, the title compound was obtained as a white solid. LCMS (ESI) m/z: 661.0 $[M+H]^+$.

Step 2:

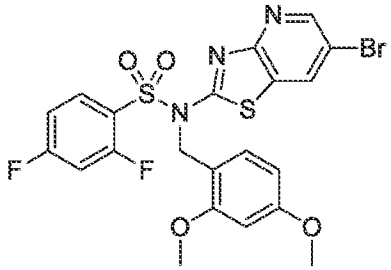
[0491] *trans*-*N*-(5-cyclopropylbenzo[*d*]isoxazol-3-yl)-1-(2-fluoro-5-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-2-oxohexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazine-6(7*H*)-sulfonamide (70 mg, 0.11 mmol) was separated by using chiral SFC (DAICEL CHIRALCEL OD-H (250 mm * 30 mm, 5 um); Supercritical CO_2 / EtOH + 0.1% $NH_3 \cdot H_2O$ = 85/15; 60 mL/min) to afford (4a*R*,8a*R*)-*N*-(5-cyclopropylbenzo[*d*]isoxazol-3-yl)-1-(2-fluoro-5-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-2-oxohexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazine-6(7*H*)-sulfonamide (13 mg, first peak) and (4a*S*,8a*S*)-*N*-(5-cyclopropylbenzo[*d*]isoxazol-3-yl)-1-(2-fluoro-5-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-2-oxohexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazine-6(7*H*)-sulfonamide (16 mg, second peak) both as a white solid. Absolute configuration was arbitrarily assigned to each enantiomer. Example **93**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.40 (s, 1H), 7.92 (s, 2H), 7.84 - 7.71 (m, 2H), 7.67 (s, 1H), 7.58 - 7.50 (m, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.40 - 7.14 (m, 2H), 4.42 - 4.25 (m, 2H), 4.04 - 3.90 (m, 1H), 3.85 - 3.62 (m, 6H), 3.06 - 2.81 (m, 2H), 2.11 - 2.01 (m, 1H), 1.55 - 1.27 (m, 2H), 1.04 - 0.95 (m, 2H), 0.71 - 0.64 (m, 2H). LCMS (ESI) m/z: 661.0 $[M+H]^+$. Example **94**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.39 (s, 1H), 7.92 (s, 2H), 7.85 - 7.71 (m, 2H), 7.66 (s, 1H), 7.57 - 7.49 (m, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.38 - 7.15 (m, 2H), 4.41 - 4.31 (m, 2H), 4.01 - 3.91 (m, 1H), 3.85 - 3.61 (m, 6H), 3.03 - 2.81 (m, 2H), 2.11 - 2.00 (m, 1H), 1.55 - 1.27 (m, 2H), 1.03 - 0.97 (m, 2H), 0.72 - 0.64 (m, 2H). LCMS (ESI) m/z: 661.0 $[M+H]^+$.

Example 95: *N*-(6-bromothiazolo[4,5-*b*]pyridin-2-yl)-4-(((1*S*,2*S*)-2-(dimethylamino)-cyclohexyl)amino)-2-fluorobenzenesulfonamide



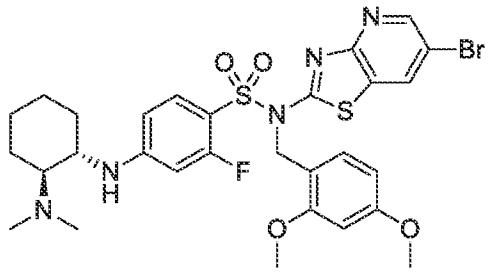
(II)

Step 1: (4a*R*,8a*R*)-*N*-(5-cyclopropylbenzo[*d*]isoxazol-3-yl)-1-(2-fluoro-5-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-2-oxohexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazine-6(7*H*)-sulfonamide and (4a*S*,8a*S*)-*N*-(5-cyclopropylbenzo[*d*]isoxazol-3-yl)-1-(2-fluoro-5-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-2-oxohexahydro-1*H*-pyrido[3,4-*b*][1,4]oxazine-6(7*H*)-sulfonamide



[0492] Following the procedure described in **Example 88** and making non-critical variations as required to replace 5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-amine with 6-bromothiazolo[4,5-*b*]pyridin-2-amine, the title compound was obtained as colorless oil. LCMS (ESI) m/z: 405.9 $[M-150+H]^+$.

Step 2: *N*-(6-bromothiazolo[4,5-*b*]pyridin-2-yl)-*N*-(2,4-dimethoxybenzyl)-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzenesulfonamide



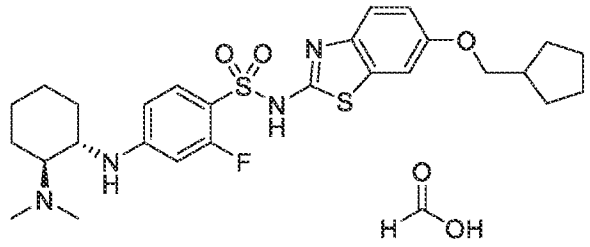
[0493] To a solution of *N*-(6-bromothiazolo[4,5-*b*]pyridin-2-yl)-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzenesulfonamide (40 mg, 0.07 mmol) in DMSO (1 mL) was added DIPEA (14 mg, 0.11 mmol) and (1*S*,2*S*)-N_1,N_1-dimethylcyclohexane-1,2-diamine (15 mg, 0.11 mmol) at room temperature. The reaction mixture was stirred at room temperature for 20 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30

mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (48 mg, crude) as yellow oil that required no further purification. LCMS (ESI) m/z: 678.2 $[M+H]^+$.

Step 3: *N*-(6-bromothiazolo[4,5-*b*]pyridin-2-yl)-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzenesulfonamide

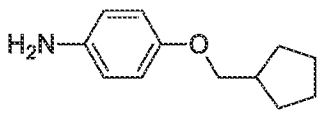
[0494] Following the procedure described in Example **88** and making non-critical variations as required to replace *N*-(5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-yl)-*N*-(2,4-dimethoxybenzyl)-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzene sulfonamide with *N*-(6-bromothiazolo[4,5-*b*]pyridin-2-yl)-*N*-(2,4-dimethoxybenzyl)-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzene sulfonamide, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J = 2.4 Hz, 1H), 8.12 (d, J = 2.4 Hz, 1H), 7.52 (t, J = 8.8 Hz, 1H), 6.50 - 6.25 (m, 2H), 6.29 - 6.20 (m, 1H), 3.72 - 3.60 (m, 1H), 3.08 - 2.92 (m, 1H), 2.59 (s, 6H), 2.05 - 1.93 (m, 2H), 1.85 - 1.75 (m, 1H), 1.67 - 1.55 (m, 1H), 1.42 - 1.17 (m, 4H), LCMS (ESI) m/z: 529.9 $[M+H]^+$.

Example 96: *N*-(6-(cyclopentylmethoxy)benzo[*d*]thiazol-2-yl)-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)-amino)-2-fluorobenzenesulfonamide formate



(II)

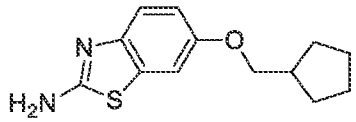
Step 1: 4-(cyclopentylmethoxy)aniline



[0495] To a stirred solution of NaH (1.32 g, 54.98 mmol, 60% in mineral oil) in DMF (20 mL) was added 4-aminophenol (2 g, 18.33 mmol) at 0 °C under nitrogen atmosphere. After stirring at 0 °C for 10 min, (bromomethyl)cyclopentane (4.48 g, 27.49 mmol) was added at 0 °C. The reaction was stirred at room temperature for 16 h. The reaction was quenched with water (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 10 - 20% EtOAc in petroleum ether) to afford the title compound (1.35 g, 39%) as black oil. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 6.77 - 6.74 (m, 2H), 6.66 - 6.63 (m, 2H), 3.76 (d, *J* = 7.2 Hz, 2H), 3.42 (s, 2H), 2.38 - 2.27 (m, 1H), 1.86 - 1.78 (m, 2H), 1.64 - 1.58 (m, 4H), 1.39 - 1.30 (m, 2H). LCMS (ESI) m/z: 192.2 $[M+H]^+$.

Step 2: 6-(cyclopentylmethoxy)benzo[*d*]thiazol-2-amine

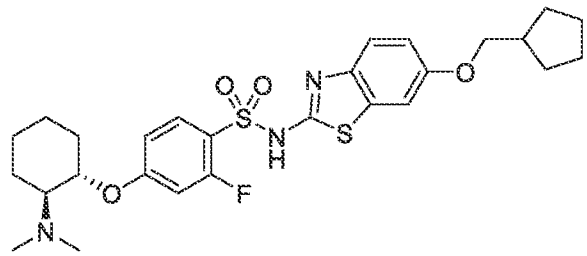


[0496] The solution of 4-(cyclopentylmethoxy)aniline (1.30 g, 7.06 mmol) and potassium thiocyanate (685 mg, 7.06 mmol) in acetic acid (7.5 mL) was stirred at 0 °C for 20 min. Bromine (0.36 mL, 7.06 mmol) in acetic acid (3.5 mL) was added slowly, maintaining the temperature below 10 °C. Then, the mixture was stirred at room temperature for 18 h. The reaction was filtered and the filter cake was washed with acetic acid (5 mL). The filtrate was concentrated in vacuo and the crude reside was diluted with hot water (5 mL) and basified to pH>11 with $NH_3•H_2O$. The resulting precipitate was filtered and the filter cake was washed with water (5 mL). The filter cake was diluted with DCM (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 14% EtOAc in petroleum ether) to afford the title compound (800 mg, 46%) as a gray solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 6.0 Hz, 1H), 6.93 - 6.90 (m, 1H), 5.22 (s, 2H), 3.84 (d, *J* = 7.2 Hz, 2H), 2.41 - 2.33 (m, 1H), 1.89 - 1.81 (m, 2H), 1.68 - 1.58 (m, 4H), 1.41 - 1.33 (m, 2H). LCMS (ESI) m/z: 249.0 $[M+H]^+$.

Step 3: *N*-(6-(cyclopentylmethoxy)benzo[*d*]thiazol-2-yl)-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzenesulfonamide formate

[0497] Following the procedure described in Example **95** and making non-critical variations as required to replace 6-bromothiazolo[4,5-*b*]pyridin-2-amine with 6-(cyclopentylmethoxy)benzo[*d*]thiazol-2-amine, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (t, *J* = 8.8 Hz, 1H), 7.26 (d, *J* = 2.4 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 6.84 - 6.81 (m, 1H), 6.42 - 6.36 (m, 3H), 3.79 (d, *J* = 6.8 Hz, 2H), 3.47 - 3.40 (m, 1H), 2.82 - 2.75 (m, 1H), 2.42 (s, 6H), 2.33 - 2.24 (m, 1H), 2.02 - 1.92 (m, 2H), 1.79 - 1.71 (m, 3H), 1.61 - 1.48 (m, 5H), 1.34 - 1.20 (m, 6H). LCMS (ESI) m/z: 547.3 $[M+H]^+$.

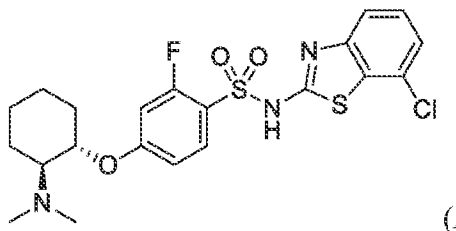
Example 97: *N*-(6-(cyclopentylmethoxy)benzo[*d*]thiazol-2-yl)-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzenesulfonamide



(II)

[0498] Following the procedure described in Example **88** and making non-critical variations as required to replace 5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-amine with 6-(cyclopentylmethoxy)benzo[*d*]thiazol-2-amine, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (t, J = 8.4 Hz, 1H), 7.24 (d, J = 2.4 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 6.97 - 6.92 (m, 1H), 6.86 - 6.83 (m, 1H), 6.82 - 6.79 (m, 1H), 4.62 - 4.56 (m, 1H), 3.79 (d, J = 7.2 Hz, 2H), 3.09 - 2.98 (m, 1H), 2.47 (s, 6H), 2.30 - 2.21 (m, 1H), 2.11 - 2.08 (m, 1H), 1.93 - 1.90 (m, 1H), 1.78 - 1.72 (m, 3H), 1.63 - 1.47 (m, 5H), 1.37 - 1.20 (m, 6H). LCMS (ESI) m/z: 548.2 $[M+H]^+$.

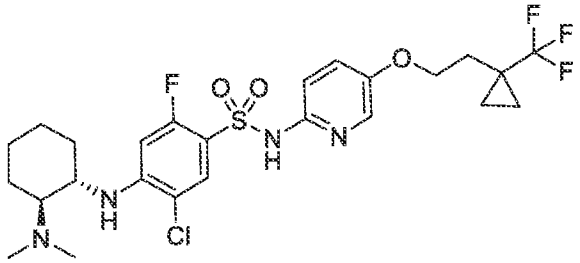
Example 99: *N*-(7-chlorobenzo[*d*]thiazol-2-yl)-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzenesulfonamide



(II)

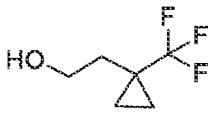
[0499] Following the procedure described in Example **88** and making non-critical variations as required to replace 5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-amine with 7-chlorobenzo[*d*]thiazol-2-amine, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (t, J = 8.8 Hz, 1H), 7.24 - 7.20 (m, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.03 - 6.97 (m, 2H), 6.92 - 6.87 (m, 1H), 4.72 - 4.64 (m, 1H), 3.43 - 3.42 (m, 1H), 2.67 (s, 6H), 2.21 - 2.12 (m, 1H), 2.07 - 2.00 (m, 1H), 1.83 - 1.73 (m, 1H), 1.67 - 1.60 (m, 1H), 1.47 - 1.20 (m, 4H). LCMS (ESI) m/z: 484.1 $[M+H]^+$.

Example 101: 5-chloro-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluoro-*N*-(5-(2-(1-(trifluoromethyl)cyclopropyl)ethoxy)pyridin-2-yl)benzenesulfonamide



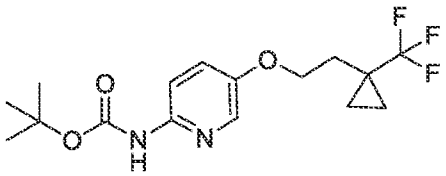
(II)

Step 1 : 2-(1-(trifluoromethyl)cyclopropyl)ethanol



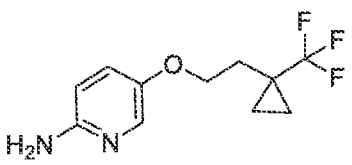
[0500] To a solution of $LiAlH_4$ (88 mg, 2.32 mmol) in THF (6 mL) was added 2-[1-(trifluoromethyl)cyclopropyl]acetic acid (300 mg, 1.78 mmol) in THF (6 mL) at room temperature. After stirring for 16 h, the reaction mixture was quenched with water (0.1 mL) and 15% aqueous NaOH solution (0.1 mL). The reaction mixture was directly dried over $MgSO_4$, filtered and concentrated under light vacuum to afford the title compound (260 mg, crude) as colorless oil that required no further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (t, J = 6.0 Hz, 2H), 1.85 (t, J = 7.2 Hz, 2H), 1.03 - 0.96 (m, 2H), 0.71 - 0.65 (m, 2H).

Step 2 : *tert*-butyl (5-(2-(1-(trifluoromethyl)cyclopropyl)ethoxy)pyridin-2-yl)carbamate



[0501] Following the procedure described in Example **1** and making non-critical variations as required to replace *tert*-butyl 3-hydroxyazetidine-1-carboxylate and pyridin-4-ol with *tert*-butyl (5-hydroxypyridin-2-yl)carbamate and 2-(1-(trifluoromethyl)cyclopropyl)ethanol, the title compound was obtained as a white solid. LCMS (ESI) m/z: 347.1 $[M+H]^+$.

Step 3 : 5-(2-(1-(trifluoromethyl)cyclopropyl)ethoxy)pyridin-2-amine

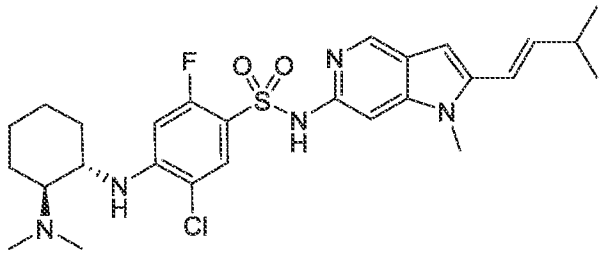


[0502] Following the procedure described in Example **1** and making non-critical variations as required to replace *tert*-butyl 3-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)piperidin-4-yl)oxy)azetidine-1-carboxylate with *tert*-butyl (5-(2-(1-(trifluoromethyl)cyclopropyl)ethoxy)pyridin-2-yl)carbamate, the title compound was obtained as a white solid. LCMS (ESI) m/z: 247.2 $[M+H]^+$.

Step 4 : 5-chloro-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluoro-*N*-(5-(2-(1-(trifluoromethyl)cyclopropyl)ethoxy)pyridin-2-yl)benzenesulfonamide

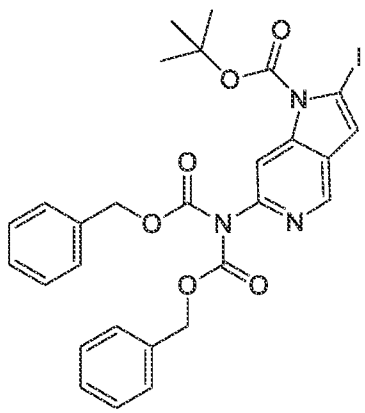
[0503] Following the procedure described in Example **88** and making non-critical variations as required to replace 5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-amine with 5-(2-(1-(trifluoromethyl)cyclopropyl)ethoxy)pyridin-2-amine, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (s, 1H), 7.62 (d, J = 6.8 Hz, 1H), 7.36 (d, J = 6.8 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 6.73 (d, J = 13.2 Hz, 1H), 5.96 (d, J = 3.2 Hz, 1H), 4.07 - 3.99 (m, 2H), 3.38 - 3.25 (m, 1H), 2.69 - 2.58 (m, 1H), 2.17 (s, 6H), 2.08 - 1.93 (m, 3H), 1.88 - 1.68 (m, 2H), 1.64 - 1.53 (m, 1H), 1.42 - 1.27 (m, 1H), 1.25 - 1.04 (m, 3H), 0.97 - 0.69 (m, 4H). LCMS (ESI) m/z: 579.1 $[M+H]^+$.

Example 102: 5-chloro-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluoro-*N*-(1-methyl-2-((*E*)-3-methylbut-1-en-1-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-yl)benzenesulfonamide



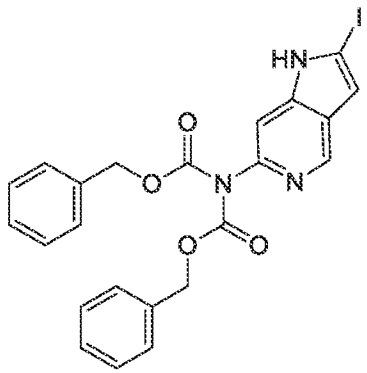
(*II*)

Step 1: *tert*-butyl 6-[bis(benzyloxycarbonyl)amino]-2-iodo-pyrrolo[3,2-*c*]pyridine-1-carboxylate



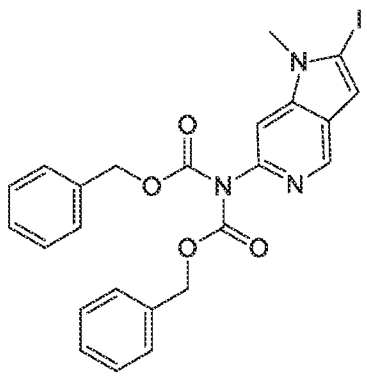
[0504] To a solution of *tert*-butyl 2-iodopyrrolo[3,2-*c*]pyridine-1-carboxylate (2.45 g, 7.12 mmol) and benzyl chloroformate (3.5 mL, 24.92 mmol) in DCM (50 mL) was added DIPEA (3.1 mL, 17.8 mmol) at 0 °C. Then, the reaction was warmed to room temperature and stirred for 16 h. The mixture was diluted with water (50 mL), extracted with DCM (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to afford the title compound (1.66 g, 37%) as yellow oil. LCMS (ESI) m/z: 628.3 $[M+H]^+$.

Step 2: benzyl *N*-benzyloxycarbonyl-*N*-(2-iodo-1*H*-pyrrolo[3,2-*c*]pyridin-6-yl)carbamate



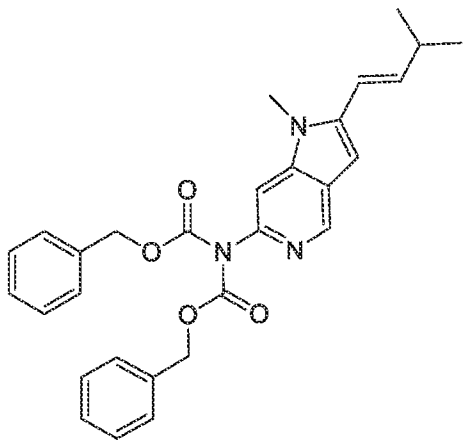
[0505] To a stirred solution of *tert*-butyl 6-[bis(benzyloxycarbonyl)amino]-2-iodo-pyrrolo[3,2-*c*]pyridine-1-carboxylate (1.7 g, 2.71 mmol) in DCM (30 mL) was added TFA (10 mL, 134.19 mmol) at room temperature and the reaction was stirred at room temperature for 2 h. The mixture was concentrated in vacuo, the crude residue was dissolved in DCM (100 mL), washed with 10% aqueous NaOH solution (50 mL) and brine (50 mL), the organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford the title compound (1.4 g, crude) as yellow oil that required no further purification. LCMS (ESI) m/z: 528.1 $[M+H]^+$.

Step 3: benzyl *N*-benzyloxycarbonyl-*N*-(2-iodo-1-methyl-pyrrolo[3,2-*c*]pyridin-6-yl)carbamate



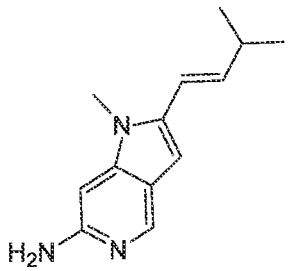
[0506] A mixture of benzyl *N*-benzyloxycarbonyl-*N*-(2-iodo-1*H*-pyrrolo[3,2-*c*]pyridin-6-yl)carbamate (1.39 g, 2.64 mmol) and cesium carbonate (1.29 g, 3.95 mmol) in DMF (25 mL) was stirred at room temperature for 30 min under nitrogen atmosphere. Then iodomethane (1.8 mL, 29.1 mmol) was added slowly. The reaction was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous NH_4Cl solution (40 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (50 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to afford the title compound (220 mg, 15%) as a yellow solid. LCMS (ESI) m/z: 542.1 $[M+H]^+$.

Step 4: benzyl *N*-benzyloxycarbonyl-*N*-[1-methyl-2-[(*E*)-3-methylbut-1-enyl]pyrrolo[3,2-*c*]pyridin-6-yl]carbamate



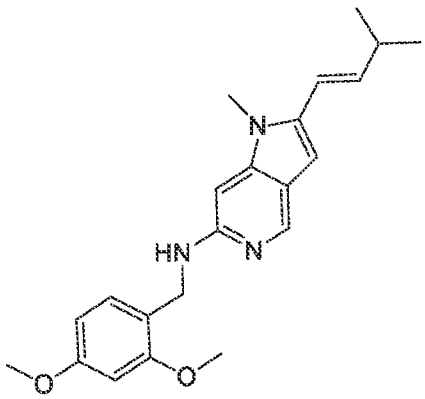
[0507] To a solution of benzyl *N*-benzyloxycarbonyl-*N*-(2-iodo-1-methyl-pyrrolo[3,2-*c*]pyridin-6-yl)carbamate (350 mg, 0.65 mmol), K_2CO_3 (178 mg, 1.29 mmol) and 4,4,5,5-tetramethyl-2-[(*E*)-3-methylbut-1-enyl]-1,3,2-dioxaborolane (300 mg, 1.53 mmol) in 1,4-dioxane (2 mL) and water (0.2 mL) was added $Pd(dppf)Cl_2$ (47 mg, 0.06 mmol). The resulting mixture was stirred at 75 °C under N_2 atmosphere for 16 h. After cooling to room temperature, the reaction was diluted with water (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to afford the title compound (120 mg, 38%) as yellow oil. LCMS (ESI) m/z: 484.3 $[M+H]^+$.

Step 5: (*E*)-1-methyl-2-(3-methylbut-1-en-1-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine



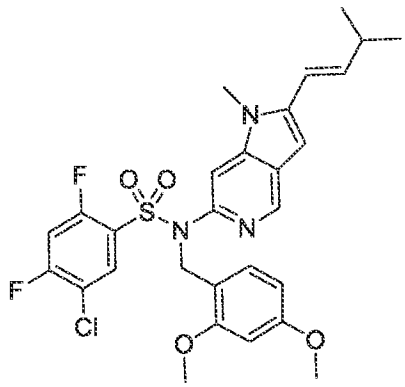
[0508] A mixture of benzyl *N*-benzyloxycarbonyl-*N*-[1-methyl-2-[(*E*)-3-methylbut-1-enyl]pyrrolo[3,2-*c*]pyridin-6-yl]carbamate (190 mg, 0.39 mmol) in EtOH (13 mL), and water (7 mL) was added KOH (1.1 g, 19.65 mmol). The reaction was stirred at 100 °C for 2 h. After cooling to room temperature, the mixture was concentrated in vacuo to remove most solvent. The crude residue was diluted with water (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (84 mg, crude) as yellow oil that required no further purification. LCMS (ESI) m/z: 216.2 $[M+H]^+$.

Step 6: (*E*)-*N*-(2,4-dimethoxybenzyl)-1-methyl-2-(3-methylbut-1-en-1-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine



[0509] Following the procedure described in Example **88** and making non-critical variations as required to replace 5-chloro-6-(cyclopentylmethoxy)benzo[*d*]isoxazol-3-amine with (*E*)-1-methyl-2-(3-methylbut-1-en-1-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine, the title compound was obtained as yellow oil. LCMS (ESI) m/z: 366.3 $[M+H]^+$.

Step 7: (*E*)-5-chloro-*N*-(2,4-dimethoxybenzyl)-2,4-difluoro-*N*-(1-methyl-2-(3-methylbut-1-en-1-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-yl)benzenesulfonamide

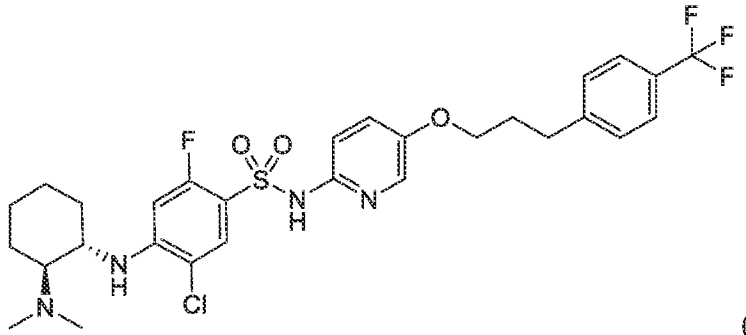


[0510] A mixture of (*E*)-*N*-(2,4-dimethoxybenzyl)-1-methyl-2-(3-methylbut-1-en-1-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (70 mg, 0.19 mmol) in MeCN (3 mL) was added 5-chloro-2,4-difluorobenzenesulfonylchloride (94 mg, 0.38 mmol) and 1,4-diazabicyclo[2.2.2]octane (43 mg, 0.38 mmol) at room temperature. The mixture was stirred at room temperature for 16 h. The reaction was diluted with water (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to afford the title compound (70 mg, 63%) as a yellow solid. LCMS (ESI) m/z: 576.2 $[M+H]^+$.

Step 8: 5-chloro-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluoro-*N*-(1-methyl-2-((*E*)-3-methylbut-1-en-1-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-yl)benzenesulfonamide

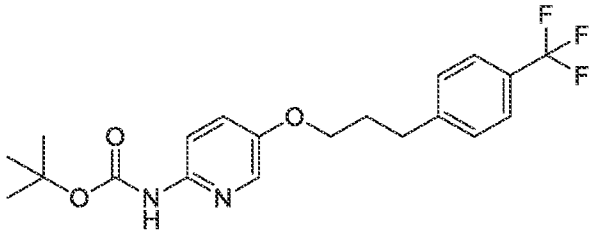
[0511] Following the procedure described in Example **95** and making non-critical variations as required to replace *N*-(6-bromothiazolo[4,5-*b*]pyridin-2-yl)-*N*-(2,4-dimethoxybenzyl)-2,4-difluorobenzenesulfonamide with (*E*)-5-chloro-*N*-(2,4-dimethoxybenzyl)-2,4-difluoro-*N*-(1-methyl-2-(3-methylbut-1-en-1-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-yl)benzenesulfonamide, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 7.70 (d, J = 7.2 Hz, 1H), 6.98 (s, 1H), 6.67 - 6.60 (m, 2H), 6.50 - 6.35 (m, 2H), 5.75 (d, J = 2.8 Hz, 1H), 3.59 (s, 3H), 3.25 - 3.18 (m, 2H), 2.61 - 2.52 (m, 1H), 2.14 (s, 6H), 2.10 - 2.03 (m, 1H), 1.83 - 1.73 (m, 2H), 1.61 - 1.52 (m, 1H), 1.40 - 1.26 (m, 1H), 1.21 - 1.15 (m, 2H), 1.11 - 1.06 (m, 7H). LCMS (ESI) m/z: 548.3 $[M+H]^+$.

Example 103: 5-chloro-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluoro-*N*-(5-(3-(4-(trifluoromethyl)phenyl)propoxy)pyridin-2-yl) benzenesulfonamide



(*II*)

Step 1: *tert*-butyl (5-(3-(4-(trifluoromethyl)phenyl)propoxy)pyridin-2-yl)carbamate

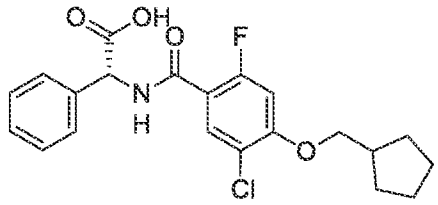


[0512] To a stirred solution of PPh_3 (390 mg, 1.48 mmol) and *tert*-butyl *N*-(5-hydroxy-2-pyridyl)carbamate (300 mg, 1.43 mmol) in THF (9 mL) was added DIAD (300 mg, 1.48 mmol) at 0 °C. The mixture was stirred for 16 h at room temperature under nitrogen atmosphere. The reaction was diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 30% EtOAc in petroleum ether) to afford the title compound (320 mg, 57%) as a white solid. LCMS (ESI) m/z: 341.1 $[M-56+H]^+$.

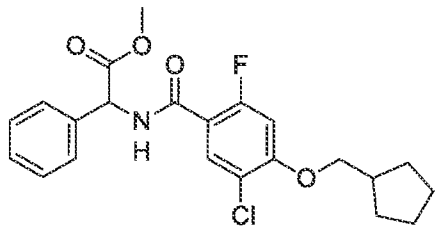
Step 2: 5-chloro-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluoro-*N*-(5-(3-(4-(trifluoromethyl)phenyl)propoxy)pyridin-2-yl) benzenesulfonamide

[0513] Following the procedure described in Example **101** and making non-critical variations as required to replace *tert*-butyl (5-(2-(1-(trifluoromethyl)cyclopropyl)ethoxy)pyridin-2-yl)carbamate with *tert*-butyl (5-(3-(4-(trifluoromethyl)phenyl)propoxy)pyridin-2-yl)carbamate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, J = 2.8 Hz, 1H), 7.66 - 7.59 (m, 2H), 7.50 - 7.41 (m, 2H), 7.40 - 7.35 (m, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 13.2 Hz, 1H), 5.98 - 5.89 (m, 1H), 3.96 (t, J = 6.4 Hz, 2H), 2.80 (t, J = 7.6 Hz, 2H), 2.65 - 2.55 (m, 1H), 2.55 - 2.50 (m, 1H), 2.16 (s, 6H), 2.07 - 1.94 (m, 3H), 1.89 - 1.69 (m, 2H), 1.65 - 1.55 (m, 1H), 1.42 - 1.27 (m, 1H), 1.26 - 1.06 (m, 3H). LCMS (ESI) m/z: 629.3 $[M+H]^+$.

Example 104: (*R*)-2-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamido)-2-phenylacetic acid

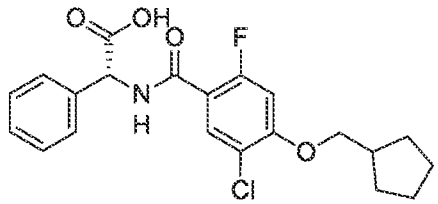


Step 1: methyl 2-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamido)-2-phenylacetate



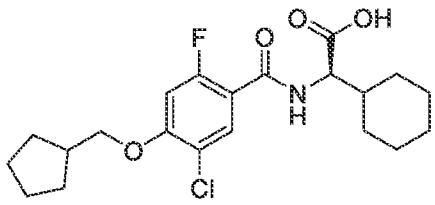
[0514] Following the procedure described in Example **1** and making non-critical variations as required to replace *tert*-butyl 3-((1-sulfamoylpiperidin-4-yl)oxy)azetidine-1-carboxylate with methyl 2-amino-2-phenylacetate hydrochloride, the title compound was obtained as colorless oil. LCMS (ESI) m/z: 420.1 $[M+H]^+$.

Step 2: (*R*)-2-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamido)-2-phenylacetic acid

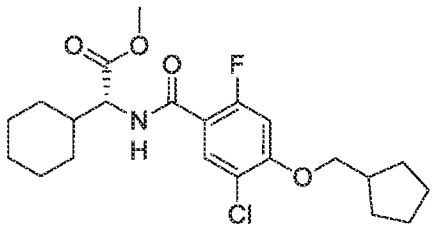


[0515] Following the procedure described in Example **75** and making non-critical variations as required to replace methyl 5-cyclopropyl-2-fluorobenzoate with methyl 2-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamido)-2-phenylacetate, 2-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamido)-2-phenylacetic acid was obtained as a white soild. The enantiomer was separated by using chiral SFC (Daicel chir Alpak As (250 mm * 30 mm, 10 um) Supercritical CO_2/EtOH + 0.1% $NH_3 \cdot H_2O$ = 35/65; 60 mL/min) to afford the title compound (29 mg, second peak) as a white solid. Absolute configuration was arbitrarily assigned to each enantiomer. ^1H NMR (400 MHz, DMSO-d_6) δ 8.80 - 8.73 (m, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.49 - 7.44 (m, 2H), 7.41 - 7.31 (m, 3H), 7.20 (d, J = 12.8 Hz, 1H), 5.35 - 5.15 (m, 1H), 4.01 (d, J = 6.8 Hz, 2H), 2.40 - 2.27 (m, 1H), 1.83 - 1.72 (m, 2H), 1.68 - 1.48 (m, 4H), 1.43 - 1.28 (m, 2H). LCMS (ESI) m/z: 406.0 $[M+H]^+$.

Example 107: (*R*)-2-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamido)-2-cyclohexyl-acetic acid



Step 1: (*R*)-methyl 2-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamido)-2-cyclohexylacetate

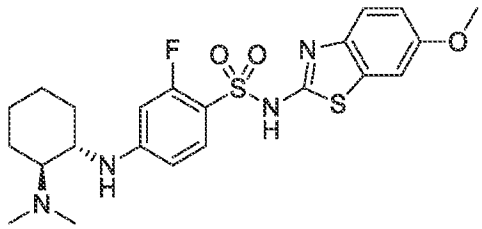


[0516] To a solution of methyl (2*R*)-2-amino-2-cyclohexyl-acetate hydrochloride (100 mg, 0.48 mmol) and 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-benzoic acid (131 mg, 0.48 mmol) in DCM (3 mL) was added DIPEA (0.26 mL, 1.44 mmol), 1-hydroxybenzotriazole (130 mg, 0.96 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimidehydrochloride (184 mg, 0.96 mmol). The reaction was stirred at room temperature for 16 h. The reaction was diluted with water (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (150 mg, crude) as yellow oil that required no further purification. LCMS (ESI) m/z: 426.1 $[M+H]^+$.

Step 2: (*R*)-2-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamido)-2-cyclohexylacetic acid

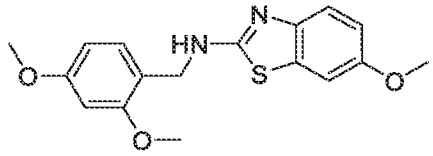
[0517] Following the procedure described in Example **104** and making non-critical variations as required to replace (*R*)-methyl 2-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamido)-2-phenylacetat*e* with (*R*)-methyl 2-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamido)-2-cyclohexylacetate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 12.76 (s, 1H), 8.26 - 8.13 (m, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 12.4 Hz, 1H), 4.35 - 4.22 (m, 1H), 4.01 (d, *J* = 6.8 Hz, 2H), 2.41 - 2.24 (m, 1H), 1.86 - 1.51 (m, 13H), 1.42 - 1.30 (m, 2H), 1.22 - 1.08 (m, 4H). LCMS (ESI) m/z: 412.1 $[M+H]^+$.

Example 201: 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluoro-*N*-(6-methoxybenzo[*d*]thiazol-2-yl)benzenesulfonamide



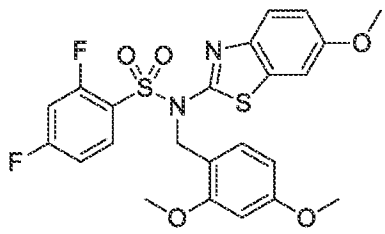
(II)

Step 1: *N*-(2,4-dimethoxybenzyl)-6-methoxybenzo[*d*]thiazol-2-amine



[0518] To a stirred solution of 6-methoxybenzo[*d*]thiazol-2-amine (500 mg, 2.77 mmol) and 2,4-dimethoxybenzaldehyde (461 g, 2.77 mmol) in DCM (20 mL) was added $TiCl(O\textit{i}\text{-}Pr)_3$ (6.38 mL, 6.38 mmol, 1 M in hexane) in one portion under nitrogen atmosphere. The solution was stirred for 10 min before the portion wise addition of $NaBH(OAc)_3$ (2.94 g, 13.87 mmol) at 0 °C. The reaction was stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (100 mL), extracted with DCM (100 mL x 3). The combined organic lawyers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 50% EtOAc in petroleum ether) to afford the title compound (620 g, 61%) as a white solid. LCMS (ESI) m/z: 331.1 $[M+H]^+$.

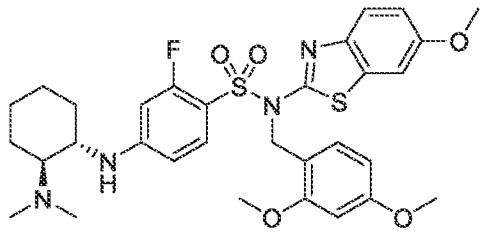
Step 2: *N*-(2,4-dimethoxybenzyl)-2,4-difluoro-*N*-(6-methoxybenzo[*d*]thiazol-2-yl)benzenesulfonamide



[0519] To a solution of *N*-(2,4-dimethoxybenzyl)-6-methoxybenzo[*d*]thiazol-2-amine (350 mg, 1.06 mmol) in THF (7 mL) was added LiHMDS (1.27 mL, 1.27 mmol, 1 M) at -78 °C. The reaction was stirred for 30 min at 0 °C and a solution of 2,4-difluorobenzenesulfonylchloride (450 mg, 2.12 mmol) in THF (4 mL) was added dropwise at -78 °C. After stirring at room temperature for 16 h, the reaction was diluted with aqueous NH_4Cl solution (15 mL) and extracted with EtOAc (20 mL x 3). The combined organic lawyers were washed with brine (30 mL), dried over

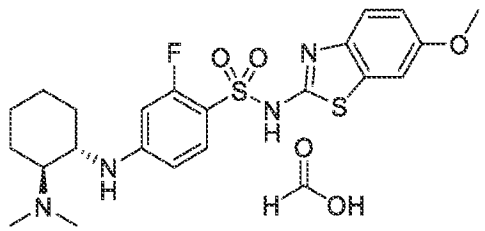
anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 10 - 30% EtOAc in petroleum ether) to afford the title compound (100 mg, 19%) as a white solid. LCMS (ESI) m/z: 507.1 $[M+H]^+$.

Step 3: *N*-(2,4-dimethoxybenzyl)-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl) amino)-2-fluoro-*N*-(6-methoxybenzo[*d*]thiazol-2-yl)benzenesulfonamide



[0520] To a stirred solution of (1*S*,2*S*)-N^1,N^1-dimethylcyclohexane-1,2-diamine (140 mg, 1 mmol) and DIPEA (127 mg, 1.0 mmol) in DMSO (2 mL) was added *N*-(2,4-dimethoxybenzyl)-2,4-difluoro-*N*-(6-methoxybenzo[*d*]thiazol-2-yl)benzenesulfonamide (100 mg, 0.2 mmol). The mixture was stirred at 60 °C for 16 h under nitrogen atmosphere. After cooling to room temperature, the reaction was quenched with sat. aq. NH_4Cl (20 mL), extracted with EtOAc (20 mL x 3). The combined organic lawyers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by prep-TLC (PE:EtOAc = 1:1) to afford the title compound (110 mg, 88%) as a white solid. LCMS (ESI) m/z: 629.3 $[M+H]^+$.

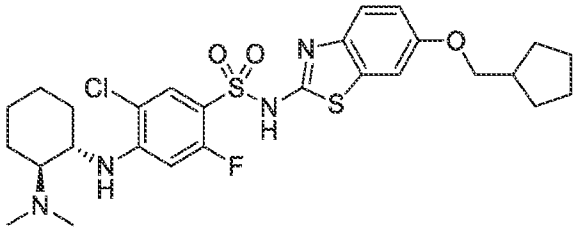
Step 4: 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluoro-*N*-(6-methoxybenzo[*d*]thiazol-2-yl)benzenesulfonamide formate



[0521] A solution of *N*-(2,4-dimethoxybenzyl)-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl) amino)-2-fluoro-*N*-(6-methoxybenzo[*d*]thiazol-2-yl)benzenesulfonamide (110 mg, 0.17 mmol) in formic acid (3 mL) was stirred at room temperature for 16 h. The mixture was concentrated in vacuo and the crude residue was purified by reverse phase chromatography (acetonitrile 15 - 45% / 0.2% formic acid in water) to afford the title compound (13 mg, 17%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.53 - 7.45 (m, 1H), 7.25 (d, J = 2.8 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 6.85 - 6.68 (m, 1H), 6.45 - 6.30 (m, 2H), 3.72 (s, 3H), 3.58 - 3.47 (m, 1H), 2.85 -

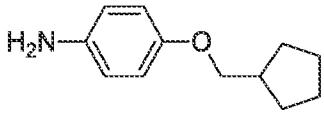
2.76 (m, 1H), 2.50 (s, 3H), 2.43 (s, 3H), 2.06 - 1.85 (m, 2H), 1.82 - 1.73 (m, 1H), 1.65 - 1.50 (m, 1H), 1.36 - 1.10 (m, 3H), 1.10 - 1.02 (m, 1H). LCMS (ESI) m/z: 479.1 $[M+H]^+$.

Example 202: 5-chloro-*N*-(6-(cyclopentylmethoxy)benzo[*d*]thiazol-2-yl)-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzenesulfonamide



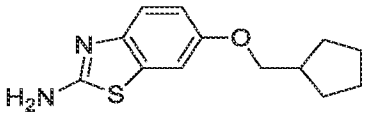
(II)

Step 1: 4-(cyclopentylmethoxy)aniline



[0522] To a stirred solution of NaH (1.32 g, 54.98 mmol, 60% in mineral oil) in DMF (20 mL) was added 4-aminophenol (2 g, 18.33 mmol) at 0 °C under nitrogen atmosphere. After stirring at 0 °C for 10 min, (bromomethyl)cyclopentane (4.48 g, 27.49 mmol) was added at 0 °C. The reaction was stirred at room temperature for 16 h. The reaction was quenched with water (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic lawyers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 10 - 20% EtOAc in petroleum ether) to afford the title compound (1.35 g, 39%) as black oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 - 6.74 (m, 2H), 6.66 - 6.63 (m, 2H), 3.76 (d, *J* = 7.2 Hz, 2H), 3.42 (s, 2H), 2.38 - 2.27 (m, 1H), 1.86 - 1.78 (m, 2H), 1.64 - 1.58 (m, 4H), 1.39 - 1.30 (m, 2H). LCMS (ESI) m/z: 192.2 $[M+H]^+$.

Step 2: 6-(cyclopentylmethoxy)benzo[*d*]thiazol-2-amine



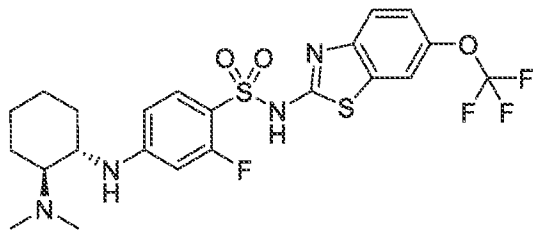
[0523] The solution of 4-(cyclopentylmethoxy)aniline (1.30 g, 7.06 mmol) and potassium thiocyanate (685 mg, 7.06 mmol) in acetic acid (7.5 mL) was stirred at 0 °C for 20 min. Bromine (0.36 mL, 7.06 mmol) in acetic acid (3.5 mL) was added slowly and kept the temperature below 10 °C. Then, the mixture was stirred at room temperature for 18 h. The reaction was filtered and the filter cake was washed with acetic acid (5 mL). The filtrate was concentrated in vacuo and the

crude reside was diluted with hot water (5 mL) and basified to pH>11 with ammonium hydroxide. The resulting precipitate was filtered and the filter cake was washed with water (5 mL). The filter cake was diluted with DCM (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 14% EtOAc in petroleum ether) to afford the title compound (800 mg, 46%) as a gray solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 6.0 Hz, 1H), 6.93 - 6.90 (m, 1H), 5.22 (s, 2H), 3.84 (d, *J* = 7.2 Hz, 2H), 2.41 - 2.33 (m, 1H), 1.89 - 1.81 (m, 2H), 1.68 - 1.58 (m, 4H), 1.41 - 1.33 (m, 2H). LCMS (ESI) m/z: 249.0 $[M+H]^+$.

Step 3: 5-chloro-*N*-(6-(cyclopentylmethoxy)benzo[*d*]thiazol-2-yl)-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzenesulfonamide

[0524] Following the procedure described in **Example 201** and making non-critical variations as required to replace difluorobenzenesulfonylchloride with 5-chloro-2,4-difluorobenzene-1-sulfonyl chloride, 6-methoxybenzo[*d*]thiazol-2-amine with 6-(cyclopentylmethoxy)benzo [*d*]thiazol-2-amine, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.13 (s, 1H), 8.69 (s, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.46 (d, *J* = 2.4 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.07 (d, *J* = 13.2 Hz, 1H), 7.01 - 6.98 (m, 1H), 6.26 (d, *J* = 10.4 Hz, 1H), 3.98 - 3.92 (m, 1H), 3.83 (d, *J* = 6.8 Hz, 2H), 3.58 - 3.47 (m, 1H), 2.75 (s, 3H), 2.60 (s, 3H), 2.32 - 2.23 (m, 1H), 2.10 - 2.02 (m, 1H), 1.91 - 1.72 (m, 4H), 1.63 - 1.49 (m, 5H), 1.43 - 1.23 (m, 6H). LCMS (ESI) m/z: 581.2 $[M+H]^+$.

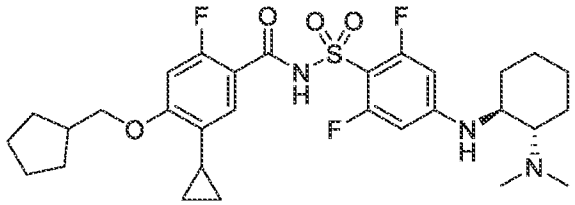
Example 203: 4-(((*1S*,*2S*)-2-(dimethylamino)cyclohexyl)amino)-2-fluoro-*N*-(6-(trifluoromethoxy)benzo[*d*]thiazol-2-yl)benzenesulfonamide



(II)

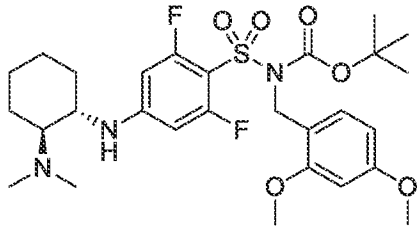
[0525] Following the procedure described in **Example 201** and making non-critical variations as required to replace 6-methoxybenzo[d]thiazol-2-amine with 6-(trifluoromethoxy)-benzo[*d*]thiazol-2-amine, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (s, 1H), 7.56 - 4.47 (m, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.14 - 7.07 (m, 1H), 6.46 - 6.31 (m, 3H), 3.68 - 3.60 (m, 1H), 3.12 - 3.00 (m, 1H), 2.61 (s, 6H), 2.06 - 1.94 (m, 2H), 1.82 - 1.73 (m, 1H), 1.66 - 1.55 (m, 1H), 1.46 - 1.08 (m, 4H). LCMS (ESI) m/z: 533.2 $[M+H]^+$.

Example 204: 4-(cyclopentylmethoxy)-5-cyclopropyl-*N*-((4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorophenyl)sulfonyl)-2-fluorobenzamide



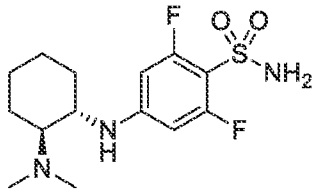
(I)

Step 1: *tert*-butyl 2,4-dimethoxybenzyl((4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)-amino)-2,6-difluorophenyl)sulfonyl)carbamate



[0526] To a stirred mixture of *tert*-butyl 2,4-dimethoxybenzyl((2,4,6-trifluorophenyl)sulfonyl)carbamate (450 mg, 0.98 mmol) and DIPEA (0.32 mL, 1.95 mmol) in DMF (5 mL) was added (1*S*,2*S*)-N^1,N^1-dimethylcyclohexane-1,2-diamine (138 mg, 0.98 mmol). After stirring at 40 °C for 2 h, the mixture was diluted with ethyl acetate (150 mL) and washed with water (50 mL x 4). The organic layer was washed with brine (50 mL), dried over anhydrous $NaSO_4$, filtered and concentrated in vacuo. The residue was purified by prep-TLC (10% MeOH in DCM) to afford the title compound (180 mg, 32%) as yellow oil. LCMS (ESI) m/z: 584.1 $[M+H]^+$.

Step 2: 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide



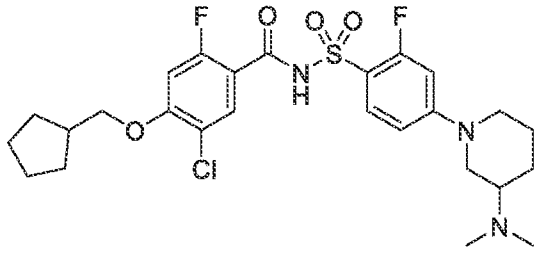
[0527] To a stirred solution of *tert*-butyl 2,4-dimethoxybenzyl((4-(((1*S*,2*S*)-2-(dimethyl-amino)cyclohexyl)amino)-2,6-difluorophenyl)sulfonyl)carbamate (180 mg, 0.31 mmol) in DCM (5 mL) was added TFA (0.5 mL, 0.31 mmol) and triethylsilane (0.51 mL, 3.22 mmol) at 20 °C. After stirring at 20 °C for 1 h, the reaction was diluted with H_2O (20 mL) and extracted with DCM (20 mL x 2). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by pre-

TLC (10% MeOH in DCM) to afford the title compound (100 mg, 97%) as a white solid. LCMS (ESI) m/z: 333.9 $[M+H]^+$.

Step 3: 4-(cyclopentylmethoxy)-5-cyclopropyl-*N*-((4-(((1*S*,2*S*)-2-(dimethylamino)-cyclohexyl)amino)-2,6-difluorophenyl)sulfonyl)-2-fluorobenzamide

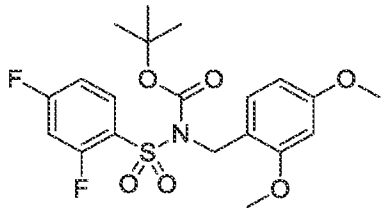
[0528] A mixture of 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide (30 mg, 0.09 mmol) and 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid (27 mg, 0.10 mmol), DMAP (11 mg, 0.09 mmol) and EDCI (19 mg, 0.099 mmol) in DCM (5 mL) was stirred at room temperature for 16 h under nitrogen atmosphere. The reaction was quenched with 10% aqueous citric acid (15 mL) and extracted with DCM (20 mL x 2). The combined organic lawyers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by reverse phase chromatography (acetonitrile 35 - 65% / (0.2% formic acid) in water) to afford the title compound (10 mg, 16%) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.35 (d, J = 8.8 Hz, 1H), 6.60 (d, J = 13.2 Hz, 1H), 6.35 (d, J = 11.6 Hz, 2H), 3.89 (d, J = 6.4 Hz, 2H), 3.75 - 3.65 (m, 1H), 3.18 - 3.10 (m, 1H), 2.78 (s, 6H), 2.46 - 2.35 (m, 1H), 2.19 - 2.08 (m, 2H), 2.05 - 1.52 (m, 10H), 1.48 - 1.36 (m, 4H), 1.29 - 1.23 (m, 1H), 0.87 - 0.83 (m, 2H), 0.67 - 0.63 (m, 2H). LCMS (ESI) m/z: 594.1 $[M+H]^+$.

Example 205: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-(3-(dimethylamino)piperidin-1-yl)-2-fluorophenyl)sulfonyl)-2-fluorobenzamide



(I)

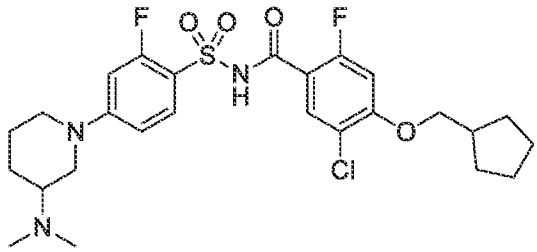
Step 1: *tert*-butyl (2,4-difluorophenyl)sulfonyl(2,4-dimethoxybenzyl)carbamate



[0529] To a stirred solution of 2,4-dimethoxybenzylamine (7.87 g, 47.04 mmol) and pyridine (19 mL, 235.18 mmol) in DCM (220 mL) was added 2,4-difluorobenzenesulfonylchloride (10.0 g, 47.04 mmol) at 0 °C. Then the reaction was stirred at room temperature for 1 h. Boc_2O (50.85 g, 233 mmol) and DMAP (5.69 g, 46.6 mmol) were added to the mixture. The reaction was stirred

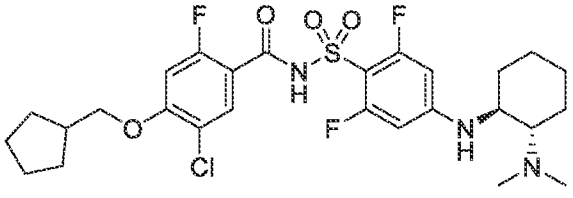
at 40 °C for 16 h. After cooling to room temperature, the reaction was diluted with water (100 mL) and extracted with DCM (150 mL x 3). The combined organic lawyers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 15% EtOAc in petroleum ether) to afford the title compound (15 g, 73%) as a yellow solid. LCMS (ESI) m/z: 466.1 $[M+Na]^+$.

Step 2: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-(3-(dimethylamino)piperidin-1-yl)-2-fluorophenyl)sulfonyl)-2-fluorobenzamide



[0530] Following the procedure described in **Example 204** and making non-critical variations as required to replace *tert*-butyl 2,4-dimethoxybenzyl((2,4,6-trifluorophenyl)sulfonyl)carbamate with *tert*-butyl (2,4-difluorophenyl)sulfonyl(2,4-dimethoxybenzyl)carbamate, 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, J = 8.0 Hz, 1H), 7.65 - 7.55 (m, 1H), 6.94 (d, J = 12.0 Hz, 1H), 6.78 - 6.70 (m, 2H), 3.98 - 3.90 (m, 1H), 3.94 (d, J = 6.8 Hz, 2H), 3.78 - 3.69 (m, 1H), 3.26 - 3.15 (m, 1H), 3.09 - 2.98 (m, 1H), 2.87 - 2.81 (m, 1H), 2.78 (s, 6H), 2.36 - 2.25 (m, 1H), 2.09 - 2.01 (m, 1H), 1.85 - 1.70 (m, 3H), 1.66 - 1.45 (m, 6H), 1.38 - 1.29 (m, 2H). LCMS (ESI) m/z: 556.1 $[M+H]^+$.

Example 206 5-chloro-4-(cyclopentylmethoxy)-N-((4-(((1S,2S)-2-(dimethylamino)-cyclohexyl)amino)-2,6-difluorophenyl)sulfonyl)-2-fluorobenzamide

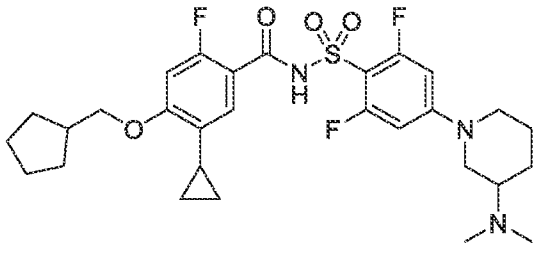


(I)

[0531] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid with 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 12.4 Hz, 1H), 6.29 (d, J = 11.6 Hz, 2H), 6.22 (d, J = 10.0 Hz, 1H), 3.94 (d, J = 6.8 Hz, 2H), 3.79 - 3.61 (m, 1H), 3.10 - 2.93

(m, 1H), 2.62 (s, 6H), 2.37 - 2.26 (m, 1H), 2.05 - 1.93 (m, 2H), 1.82 - 1.71 (m, 3H), 1.64 - 1.50 (m, 5H), 1.39 - 1.20 (m, 5H), 1.18 - 1.02 (m, 1H). LCMS (ESI) m/z: 588.1 $[M+H]^+$.

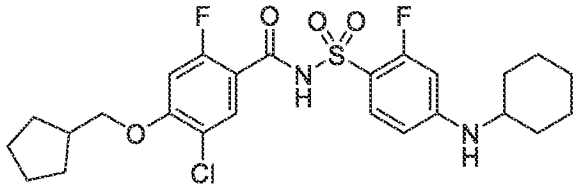
Example 207: 4-(cyclopentylmethoxy)-5-cyclopropyl-*N*-((4-(3-(dimethylamino)piperidin-1-yl)-2,6-difluorophenyl)sulfonyl)-2-fluorobenzamide



(I)

[0532] Following the procedure described in **Example 204** and making non-critical variations as required to replace (1*S*,2*S*)-N^1,N^1-dimethylcyclohexane-1,2-diamine with *N*,*N*-dimethyl-piperidin-3-amine, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.22 (d, J = 8.8 Hz, 1H), 6.68 (d, J = 12.8 Hz, 1H), 6.58 (d, J = 12.4 Hz, 2H), 4.00 - 3.90 (m, 1H), 3.88 (d, J = 6.8 Hz, 2H), 3.78 (m, 1H), 3.20 - 3.10 (m, 1H), 3.07 - 2.97 (m, 1H), 2.86 - 2.78 (m, 1H), 2.75 (s, 6H), 2.37 - 2.25 (m, 1H), 2.09 - 1.92 (m, 2H), 1.84 - 1.71 (m, 3H), 1.67 - 1.46 (m, 6H), 1.45 - 1.32 (m, 2H), 0.89 - 0.79 (m, 2H), 0.59 - 0.49 (m, 2H). LCMS (ESI) m/z: 580.3 $[M+H]^+$.

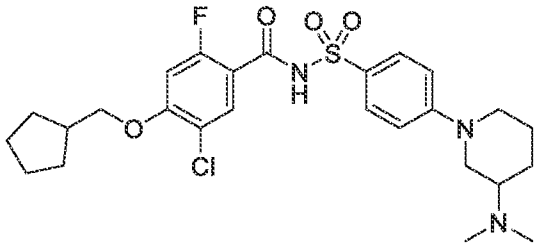
Example 208: 5-chloro-*N*-((4-(cyclohexylamino)-2-fluorophenyl)sulfonyl)-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

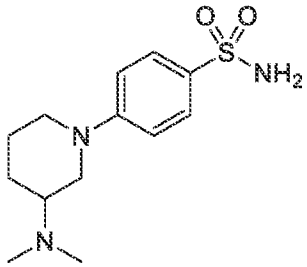
[0533] Following the procedure described in **Example 205** and making non-critical variations as required to replace *N*,*N*-dimethylpiperidin-3-amine with cyclohexanamine, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.39 (s, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.58 - 7.48 (m, 1H), 7.19 (d, J = 12.4 Hz, 1H), 6.91 (d, J = 7.2 Hz, 1H), 6.51 - 6.39 (m, 2H), 4.01 (d, J = 6.8 Hz, 2H), 3.30 - 3.20 (m, 1H), 2.38 - 2.27 (m, 1H), 1.92 - 1.84 (m, 2H), 1.80 - 1.65 (m, 4H), 1.64 - 1.49 (m, 5H), 1.40 - 1.28 (m, 4H), 1.24 - 1.13 (m, 3H). LCMS (ESI) m/z: 527.0 $[M+H]^+$.

Example 209 5-chloro-4-(cyclopentylmethoxy)-N-((4-(3-(dimethylamino)piperidin-1-yl)phenyl)sulfonyl)-2-fluorobenzamide



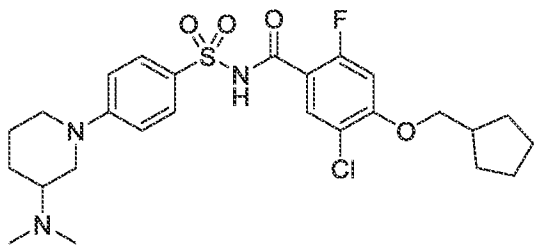
(I)

Step 1: 4-(3-(dimethylamino)piperidin-1-yl)benzenesulfonamide



[0534] A solution of *N,N*-dimethylpiperidin-3-amine (439 mg, 3.4 mmol) and 4-fluorobenzenesulfonamide (500 mg, 2.9 mmol) in DMSO (27 mL) was stirred at 100 °C for 16 h. After cooling to room temperature, the reaction was purified by reverse phase chromatography (acetonitrile 10 - 40% / 0.05% $NH_3 \cdot H_2O$ in water) to afford the title compound (210 mg, 26%) as a yellow soild. LCMS (ESI) m/z: 284.2 $[M+H]^+$.

Step 2: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-(3-(dimethylamino)piperidin-1-yl)phenyl)sulfonyl)-2-fluorobenzamide



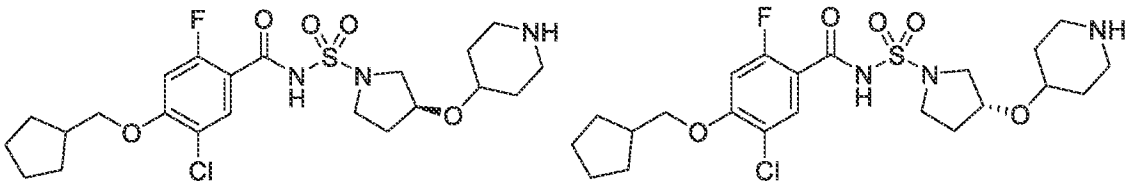
[0535] Following the procedure described in **Example 205** and making non-critical variations as required to replace 4-(3-(dimethylamino)piperidin-1-yl)-2-fluorobenzenesulfonamide with 4-(3-(dimethylamino)piperidin-1-yl)benzenesulfonamide, the title compound was obtained as a white solid. LCMS (ESI) m/z: 538.2 $[M+H]^+$.

Step 3:

[0536] 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-(3-(dimethylamino)piperidin-1-yl)phenyl)sulfonyl)-2-fluorobenzamide (200 mg, 0.37 mmol) was separated by using chiral SFC

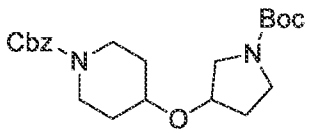
(Chiralpak PAK-AS (250 mm * 30 mm, 5 um), Supercritical CO_2 / MeOH + 0.1% $NH_3 \cdot H_2O$ = 50/50; 80 mL/min) to afford (*S*)-5-chloro-4-(cyclopentylmethoxy)-*N*-((4-(3-(dimethylamino)piperidin-1-yl)phenyl)sulfonyl)-2-fluorobenzamide (50 mg, second peak) as a white solid. Absolute configuration was arbitrarily assigned to each enantiomer. ^{1}H NMR (400 MHz, DMSO-d_6) δ ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.8 Hz, 2H), 6.97 - 6.92 (m, 3H), 3.94 (d, J = 6.8 Hz, 2H), 3.94 - 3.85 (m, 1H), 3.74 - 3.64 (m, 1H), 3.12 - 3.02 (m, 1H), 3.01 - 2.90 (m, 1H), 2.83 - 2.75 (m, 1H), 2.73 (s, 6H), 2.35 - 2.27 (m, 1H), 2.08 - 2.00 (m, 1H), 1.84 - 1.70 (m, 3H), 1.65 - 1.42 (m, 6H), 1.39 - 1.27 (m, 2H). LCMS (ESI) m/z: 538.1 $[M+H]^+$.

Example 212: and Example 213: (*S*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-(piperidin-4-yloxy)pyrrolidin-1-yl)sulfonyl)benzamide, and (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-(piperidin-4-yloxy)pyrrolidin-1-yl)sulfonyl)benzamide



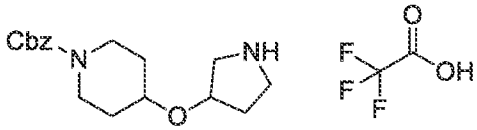
(I)

Step 1: benzyl 4-((1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)oxy)piperidine-1-carboxylate



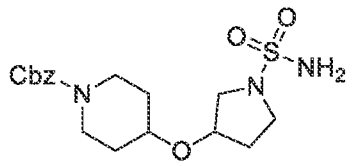
[0537] Benzyl chloroformate (0.22 mL, 1.63 mmol) was added dropwise to a stirred mixture of *tert*-butyl 3-(piperidin-4-yloxy)pyrrolidine-1-carboxylate (400 mg, 1.48 mmol) and triethylamine (0.21 mL, 1.48 mmol) in DCM (10 mL). The mixture was stirred at 20 °C for 16 h. The mixture was diluted in sat. aq. $NaHCO_3$ (20 mL), extrated with DCM (30 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by flash column chromatography eluting (solvent gradient: 0 - 50% EtOAc in petroleum ether) to afford the title compound (390 mg, 65%) as a colorless oil. LCMS (ESI) m/z: 305.2 $[M-100+H]^+$

Step 2: benzyl 4-(pyrrolidin-3-yloxy)piperidine-1-carboxylate 2,2,2-trifluoroacetate



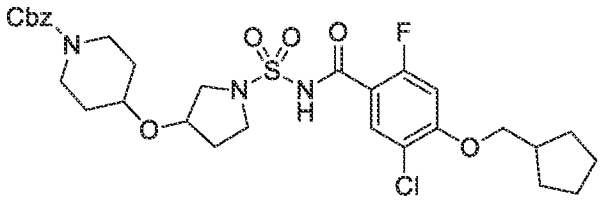
[0538] To a solution of benzyl 4-((1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl)oxy)piperidine-1-carboxylate (390 mg, 0.96 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL, 26.93 mmol) at 25 °C. The mixture was stirred at 25 °C for 1 h. The mixture was concentrated in vacuo to afford the title compound (300 mg, 74%) as a yellow solid. LCMS (ESI) m/z: 305.2 $[M+H]^+$

Step 3: benzyl 4-((1-sulfamoylpyrrolidin-3-yl)oxy)piperidine-1-carboxylate



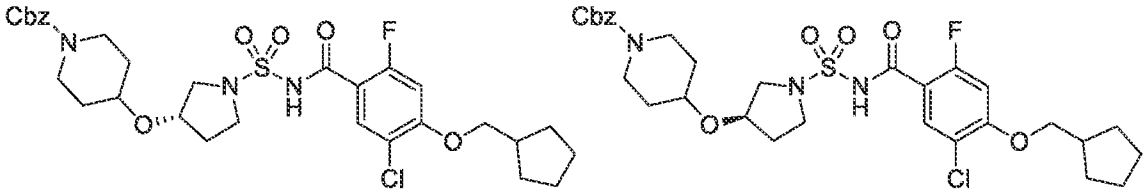
[0539] To a mixture of benzyl 4-(pyrrolidin-3-yloxy)piperidine-1-carboxylate 2,2,2-trifluoroacetate (300 mg, 0.99 mmol) in 1,4-dioxane (3.6 mL) was added sulfamide (237 mg, 2.46 mmol). The mixture was stirred at 110 °C for 16 h under nitrogen atmosphere. After cooling to room temperature, the reaction was diluted with water (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic lawyers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (320 mg, crude) as a yellow solid that required no further purification. LCMS (ESI) m/z: 385.1 $[M+H]^+$.

Step 4: benzyl 4-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)-pyrrolidin-3-yl)oxy)piperidine-1-carboxylate



[0540] To a mixture of benzyl 4-(1-sulfamoylpyrrolidin-3-yl)oxypiperidine-1-carboxylate (316 mg, 0.83 mmol) and DMAP (134 mg, 1.1 mmol) in DCM (5 mL) was added 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-benzoic acid (150 mg, 0.55 mmol) and EDCI (116 mg, 0.61 mmol). The resulting mixture was stirred at 20 °C for 2 h under nitrogen atmosphere. The reaction was extracted with DCM (30 mL x 2). The organic layers were washed with washed with 10% citric aqueous solution (10 mL x 2) and brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash column chromatography eluting (solvent gradient: 0 - 50% EtOAc in petroleum ether) to afford the title compound (150 mg, 43%) as a yellow solid. LCMS (ESI) m/z: 638.2 $[M+H]^+$.

Step 5: (*S*)-benzyl 4-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)pyrrolidin-3-yl)oxy)piperidine-1-carboxylate, and (*R*)-benzyl 4-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)pyrrolidin-3-yl)oxy)piperidine-1-carboxylate



[0541] Benzyl 4-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)-sulfamoyl)pyrrolidin -3-yl)oxy)piperidine-1-carboxylate (150 mg, 0.24 mmol) was separated by using chiral SFC (DAICEL CHIRALCEL OD-H (250mm*30mm,5um); Supercritical CO_2 / EtOH + 0.1% NH_3•H_2O = 65/35; 2.8 ml/min) to afford (*S*)-benzyl 4-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)pyrrolidin-3-yl)oxy)piperidine-1-carboxylate (70 mg, first peak) as a white solid and (*R*)-benzyl 4-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)pyrrolidin-3-yl)oxy)piperidine-1-carboxylate (70 mg, second peak) as a white solid. Absolute configuration was arbitrarily assigned to each enantiomer.

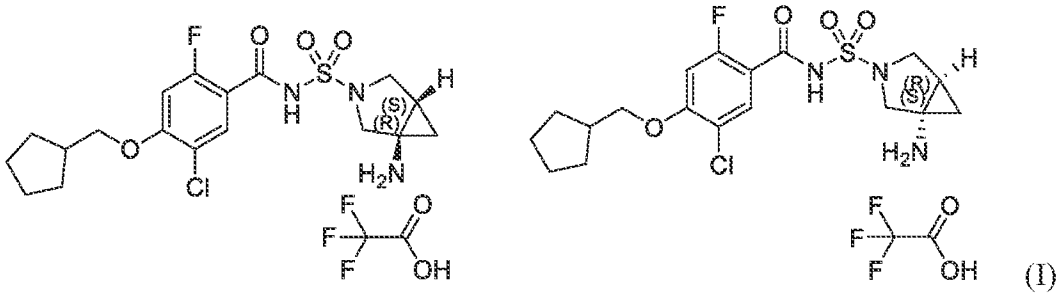
Step 6: (*S*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-(piperidin-4-yloxy)-pyrrolidin-1-yl)sulfonyl)benzamide and (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-(piperidin-4-yloxy)pyrrolidin-1-yl)sulfonyl)benzamide

[0542] A solution of (*S*)-benzyl 4-((1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)pyrrolidin-3-yl)oxy)piperidine-1-carboxylate (35 mg, 0.05 mmol) in DCM (1.5 mL) was added $PdCl_2$ (9.73 mg, 0.05 mmol). After stirring at room temperature for 16 h under hydrogen atmosphere (15 psi), the reaction was filtered through Celite and concentrated in vacuo. The residue was purified by reverse phase chromatography (acetonitrile 28 - 58% / (0.2% formic acid) in water) to afford (*S*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-(piperidin-4-yloxy)pyrrolidin-1-yl)sulfonyl) benzamide (2 mg, 8%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 12.4 Hz, 1H), 4.21 - 4.15 (m, 1H), 3.94 (d, J = 6.8 Hz, 2H), 3.64 - 3.57 (m, 1H), 3.45 - 3.35 (m, 2H), 3.27 - 3.11 (m, 3H), 3.02 - 2.78 (m, 3H), 2.34 - 2.26 (m, 1H), 2.03 - 1.85 (m, 3H), 1.81 - 1.66 (m, 3H), 1.65 - 1.47 (m, 6H), 1.41 - 1.29 (m, 2H). LCMS (ESI) m/z: 504.1 $[M+H]^+$.

[0543] Following the same procedure, (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-(piperidin-4-yloxy)pyrrolidin-1-yl)sulfonyl)benzamide was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 12.4 Hz, 1H), 4.21 - 4.15 (m, 1H),

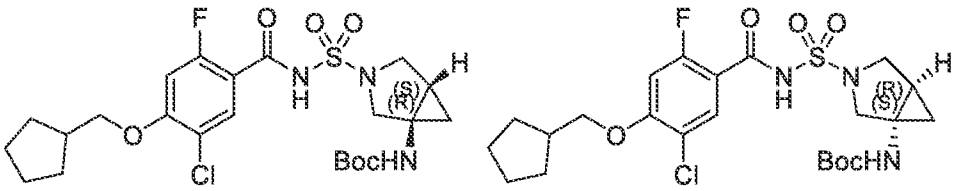
3.94 (d, J = 6.8 Hz, 2H), 3.65 - 3.57 (m, 1H), 3.45 - 3.35 (m, 2H), 3.27 - 3.10 (m, 3H), 3.03 - 2.78 (m, 3H), 2.34 - 2.28 (m, 1H), 2.02 - 1.87 (m, 3H), 1.79 - 1.68 (m, 3H), 1.63 - 1.50 (m, 6H), 1.39 - 1.31 (m, 2H). LCMS (ESI) m/z: 504.1 $[M+H]^+$.

Example 217: and Example 218: *N*-(((1*R*,5*S*)-1-amino-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide 2,2,2-trifluoroacetate, and *N*-(((1*S*,5*R*)-1-amino-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide 2,2,2-trifluoroacetate



(I)

Step 1: *tert*-butyl ((1*R*,5*S*)-3-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)-3-azabicyclo[3.1.0]hexan-1-yl)carbamate and *tert*-butyl ((1*S*,5*R*)-3-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)-3-azabicyclo[3.1.0]hexan-1-yl)carbamate

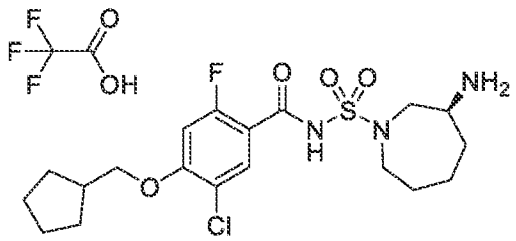


[0544] Following the procedure described in **Example 31:** and making non-critical variations as required to replace *tert*-butyl 3-(azetidin-3-yloxy)pyrrolidine-1-carboxylate with *tert*-butyl (3-azabicyclo[3.1.0]hexan-1-yl)carbamate, *tert*-butyl 3-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)-3-azabicyclo[3.1.0]hexan-1-yl)carbamate was obtained as a white solid. 3-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)-3-azabicyclo[3.1.0]hexan-1-yl)carbamate (140 mg, 0.26 mmol) was separated by using chiral SFC (DAICEL CHIRALPAK IC (250 mm * 30 mm, 5 um), Supercritical CO_2 / EtOH + 0.1% $NH_3 \cdot H_2O$ = 70/30; 60 mL/min) to afford *tert*-butyl ((1*R*,5*S*)-3-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)-3-azabicyclo[3.1.0]hexan-1-yl)carbamate (50 mg, first peak) as a yellow solid and *tert*-butyl ((1*S*,5*R*)-3-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)-3-azabicyclo[3.1.0]hexan-1-yl)carbamate (70 mg, second peak) as a yellow solid. Absolute configuration was arbitrarily assigned to each enantiomer.

Step 2: *N*-(((1*R*,5*S*)-1-amino-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide 2,2,2-trifluoroacetate, and *N*-(((1*S*,5*R*)-1-amino-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide 2,2,2-trifluoroacetate

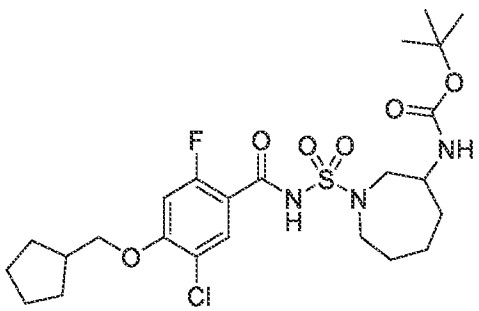
[0545] Following the procedure described in **Example 69** and making non-critical variations as required to replace (*S*)-*tert*-butyl 3-(4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)phenoxy)pyrrolidine-1-carboxylate with *tert*-butyl ((1*R*,5*S*)-3-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)-3-azabicyclo[3.1.0]hexan-1-yl)carbamate and *tert*-butyl ((1*S*,5*R*)-3-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)-3-azabicyclo[3.1.0]hexan-1-yl)carbamate, the title compounds were obtained as white solids. **Example 217**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 8.51 (s, 2H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 12.8 Hz, 1H), 4.03 (d, *J* = 7.2 Hz, 2H), 3.78 (d, *J* = 9.6 Hz, 1H), 3.68 - 3.55 (m, 2H), 3.43 (d, *J* = 9.6 Hz, 1H), 2.35 - 2.25 (m, 1H), 2.02 - 1.88 (m, 1H), 1.85 - 1.70 (m, 2H), 1.68 - 1.50 (m, 4H), 1.41 - 1.30 (m, 2H), 1.29 - 1.10 (m, 1H), 0.81 - 0.74 (m, 1H). LCMS (ESI) m/z: 432.1 $[M+H]^+$. **Example 218**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 8.53 (s, 2H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 12.4 Hz, 1H), 4.03 (d, *J* = 6.8 Hz, 2H), 3.78 (d, *J* = 9.6 Hz, 1H), 3.70 - 3.55 (m, 2H), 3.43 (d, *J* = 9.6 Hz, 1H), 2.40 - 2.25 (m, 1H), 2.02 - 1.93 (m, 1H), 1.85 - 1.69 (m, 2H), 1.68 - 1.46 (m, 4H), 1.42 - 1.30 (m, 2H), 1.28 - 1.19 (m, 1H), 0.80 - 0.70 (m, 1H). LCMS (ESI) m/z: 432.2 $[M+H]^+$.

Example 219: (*S*)-*N*-((3-aminoazepan-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide 2,2,2-trifluoroacetate



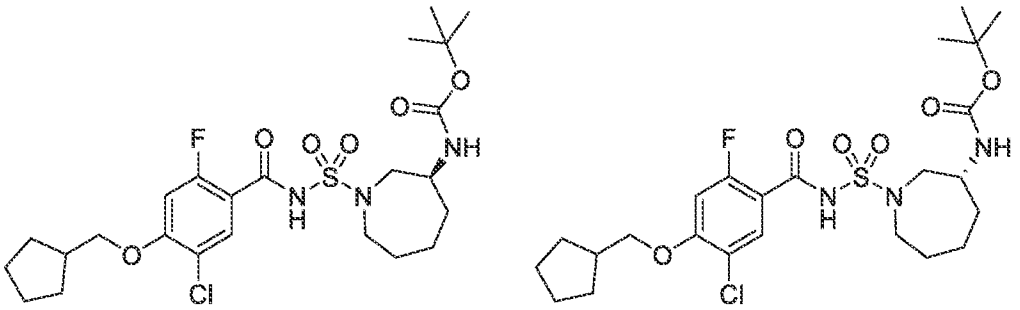
(I)

Step 1: *tert*-butyl (1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl) azepan-3-yl)carbamate



[0546] Following the procedure described in **Example 31:** and making non-critical variations as required to replace *tert*-butyl 3-(azetidin-3-yloxy)pyrrolidine-1-carboxylate with *tert*-butyl azepan-3-ylcarbamate, the title compound was obtained as a white solid.

Step 2: *tert*-butyl (*S*)-(1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)-sulfamoyl)azepan-3-yl)carbamate, and *tert*-butyl (*R*)-(1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)azepan-3-yl)carbamate

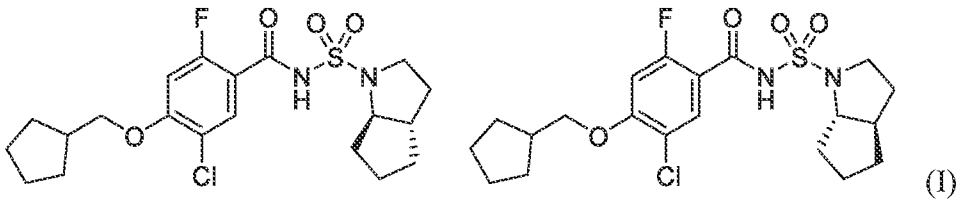


[0547] *tert*-butyl (1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl) azepan-3-yl)carbamate (140 mg, 0.26 mmol) was separated by using chiral SFC (DAICEL CHIRALPAK IC (250 mm * 30 mm, 5 um), Supercritical CO_2 / EtOH + 0.1% $NH_3 \cdot H_2O$ = 70/30; 60 mL/min) to afford *tert*-butyl ((1*R*,5*S*)-3-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)-3-azabicyclo[3.1.0]hexan-1-yl)carbamate (50 mg, first peak) as a yellow solid and *tert*-butyl ((1*S*,5*R*)-3-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)-3-azabicyclo[3.1.0]hexan-1-yl)carbamate (70 mg, second peak) as a yellow solid. Absolute configuration was arbitrarily assigned to each enantiomer.

Step 3: (*S*)-*N*-((3-aminoazepan-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide 2,2,2-trifluoroacetate

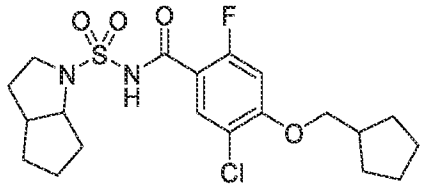
[0548] Following the procedure described in **Example 69** and making non-critical variations as required to replace (*S*)-*tert*-butyl 3-(4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)phenoxy)pyrrolidine-1-carboxylate with *tert*-butyl (*S*)-(1-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)azepan-3-yl)carbamate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 2H), 7.80 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 12.4 Hz, 1H), 3.96 (d, J = 6.8 Hz, 2H), 3.90 - 3.80 (m, 1H), 3.33 - 3.18 (m, 3H), 3.12 - 3.00 (m, 1H), 2.93 - 2.80 (m, 1H), 2.38 - 2.25 (m, 1H), 1.84 - 1.70 (m, 4H), 1.70 - 1.60 (m, 3H), 1.59 - 1.49 (m, 3H), 1.49 - 1.41 (m, 2H), 1.40 - 1.26 (m, 2H). LCMS (ESI) m/z: 448.4 $[M+H]^+$.

Example 220 and Example 221: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(((3a*S*,6a*R*)-hexahydrocyclopenta[*b*]pyrrol-1(2*H*)-yl)sulfonyl)benzamide, and 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(((3a*R*,6a*S*)-hexahydrocyclopenta[*b*]pyrrol-1(2*H*)-yl)sulfonyl)benzamide



(I)

Step 1: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((hexahydrocyclopenta[*b*]pyrrol-1(2*H*)-yl)sulfonyl)benzamide



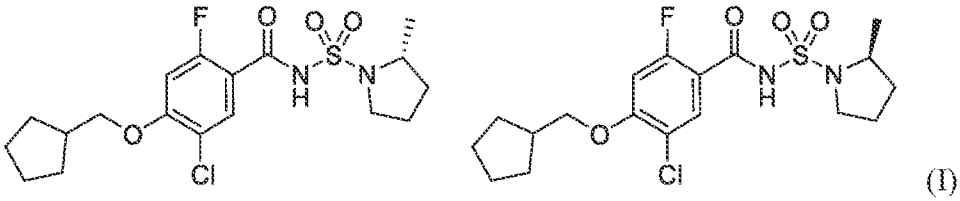
[0549] Following the procedure described in **Example 31:** and making non-critical variations as required to replace *tert*-butyl 3-(azetidin-3-yloxy)pyrrolidine-1-carboxylate with octahydrocyclopenta[*b*]pyrrole, the title compound was obtained as a white solid. LCMS (ESI) m/z: 445.0 $[M+H]^+$.

Step 2: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(((3a*S*,6a*R*)-hexahydrocyclopenta[*b*]pyrrol-1(2*H*)-yl)sulfonyl)benzamide, and 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(((3a*R*,6a*S*)-hexahydrocyclopenta[*b*]pyrrol-1(2*H*)-yl)sulfonyl)benzamide

[0550] 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((hexahydrocyclopenta[*b*]pyrrol-1(2*H*)-yl)sulfonyl)benzamide (146 mg, 0.33 mmol) was separated by using chiral SFC (DAICEL CHIRALCEL OD-H (250 mm * 30 mm, 5 um), Supercritical CO_2 / EtOH + 0.1% $NH_3 \cdot H_2O$ = 50/50; 80 mL/min) to afford 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(((3a*R*,6a*S*)-hexahydrocyclopenta[*b*]pyrrol-1(2*H*)-yl)sulfonyl)benzamide (25 mg, first peak) as a white solid and 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(((3a*S*,6a*R*)-hexahydrocyclopenta [*b*]pyrrol-1(2*H*)-yl)sulfonyl)benzamide (68 mg, second peak) as a white solid. Absolute configuration was arbitrarily assigned to each enantiomer. **Example 220**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 12.4 Hz, 1H), 4.33 - 4.26 (m, 1H), 4.02 (d, J = 6.8 Hz, 2H), 3.63 - 3.53 (m, 1H), 3.39 - 3.30 (m, 1H), 2.74 - 2.67 (m, 1H), 2.35 - 2.29 (m, 1H), 1.89 - 1.51 (m, 13H), 1.42 - 1.31 (m, 3H). LCMS (ESI) m/z: 445.0 $[M+H]^+$. **Example 221**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.78 (s, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 12.4 Hz, 1H), 4.32 -

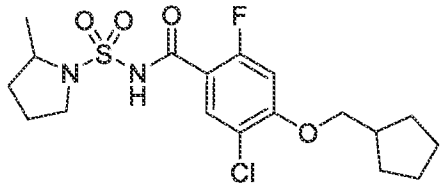
4.25 (m, 1H), 4.02 (d, *J* = 6.8 Hz, 2H), 3.62 - 3.54 (m, 1H), 3.40 - 3.34 (m, 1H), 2.73 - 2.66 (m, 1H), 2.37 - 2.28 (m, 1H), 1.86 - 1.52 (m, 13H), 1.42 - 1.28 (m, 3H). LCMS (ESI) m/z: 445.0 $[M+H]^+$.

Example 222 and Example 223: (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methylpyrrolidin-1-yl)sulfonyl)benzamide, and (*S*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methylpyrrolidin-1-yl)sulfonyl)-benzamide



(I)

Step 1: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methylpyrrolidin-1-yl)sulfonyl)benzamide



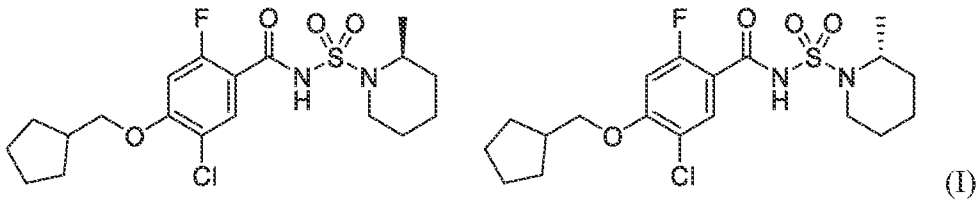
[0551] Following the procedure described in **Example 31:** and making non-critical variations as required to replace *tert*-butyl 3-(azetidin-3-yloxy)pyrrolidine-1-carboxylate with 2-methylpyrrolidine, the title compound was obtained as a white solid. LCMS (ESI) m/z: 419.2 $[M+H]^+$.

Step 2: (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methylpyrrolidin-1-yl)-sulfonyl)benzamide, and (*S*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methylpyrrolidin-1-yl)sulfonyl)-benzamide

[0552] 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methylpyrrolidin-1-yl)sulfonyl)benzamide (50 mg, 0.12 mmol) was separated by using chiral SFC (DAICEL CHIRALPAK IC (250 mm * 30 mm, 5 um), Supercritical CO_2 / EtOH + 0.1% $NH_3 \cdot H_2O$ = 75/25; 60 mL/min) to afford (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methylpyrrolidin-1-yl)sulfonyl)benzamide (6 mg, first peak) as a white solid and (*S*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methylpyrrolidin-1-yl)sulfonyl)benzamide (6 mg, second peak) as a white solid. Absolute configuration was arbitrarily assigned to each enantiomer. **Example 222:**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 12.4 Hz, 1H), 4.18 - 4.07 (m, 1H), 4.02 (d, *J* = 6.8 Hz, 2H), 3.54 - 3.44 (m, 1H), 3.40 -

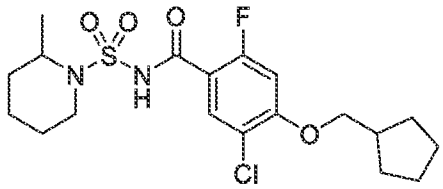
3.35 (m, 1H), 2.38 - 2.28 (m, 1H), 2.01 - 1.84 (m, 2H), 1.83 - 1.70 (m, 3H), 1.67 - 1.45 (m, 5H), 1.42 - 1.28 (m, 2H), 1.19 (d, J = 6.4 Hz, 3H). LCMS (ESI) m/z: 441.0 $[M+Na]^+$. **Example 223:**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 12.4 Hz, 1H), 4.17 - 4.07 (m, 1H), 4.02 (d, J = 6.8 Hz, 2H), 3.54 - 3.45 (m, 1H), 3.40 - 3.35 (m, 1H), 2.40 - 2.29 (m, 1H), 2.02 - 1.84 (m, 2H), 1.83 - 1.71 (m, 3H), 1.65 - 1.50 (m, 5H), 1.39 - 1.30 (m, 2H), 1.19 (d, J = 6.4 Hz, 3H). LCMS (ESI) m/z: 441.0 $[M+Na]^+$.

Example 224: and Example 225: (*S*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methylpiperidin-1-yl)sulfonyl)benzamide, and (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methylpiperidin-1-yl)sulfonyl)-benzamide



(I)

Step 1: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methylpiperidin-1-yl)sulfonyl)benzamide



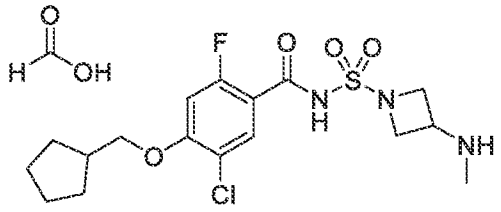
[0553] Following the procedure described in **Example 31:** and making non-critical variations as required to replace *tert*-butyl 3-(azetidin-3-yloxy)pyrrolidine-1-carboxylate with 2-methylpiperidine, the title compound was obtained as a white solid. LCMS (ESI) m/z: 433.2 $[M+H]^+$.

Step 2: (*S*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methylpiperidin-1-yl)sulfonyl)benzamide, and (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methylpiperidin-1-yl)sulfonyl)-benzamide

[0554] 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methylpiperidin-1-yl)sulfonyl)benzamide (190 mg, 0.44 mmol) was separated by using chiral SFC (DAICEL CHIRALPCEL OD-H (250 mm * 30 mm, 5 um), Supercritical CO_2 / EtOH + 0.1% $NH_3 \cdot H_2O$ = 50/50; 80 mL/min) to afford (*S*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methylpiperidin-1-yl)sulfonyl)benzamide (58 mg, first peak) as a white solid and (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methylpiperidin-1-yl)sulfonyl)benzamide (47 mg, second

peak) as a white solid. Absolute configuration was arbitrarily assigned to each enantiomer. **Example 224:**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.81 (s, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 12.4 Hz, 1H), 4.18 - 4.08 (m, 1H), 4.02 (d, J = 6.8 Hz, 2H), 3.72 - 3.63 (m, 1 H), 3.13 (t, J = 11.2 Hz, 1H), 2.40 - 2.28 (m, 1 H), 1.80 - 1.76 (m, 2 H), 1.68 - 1.38 (m, 9H), 1.35 - 1.28 (m, 3H), 1.18 (d, J = 6.8 Hz, 3H). LCMS (ESI) m/z: 433.0 $[M+H]^+$. **Example 225:**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.81 (s, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 12.4 Hz, 1H), 4.18 - 4.06 (m, 1H), 4.02 (d, J = 6.8 Hz, 2H), 3.75 - 3.60 (m, 1H), 3.14 (t, J = 11.2 Hz, 1H), 2.36 - 2.25 (m, 1 H), 1.80 - 1.76 (m, 2 H), 1.66 - 1.40 (m, 9H), 1.38 - 1.28 (m, 3H), 1.18 (d, J = 6.8 Hz, 3H). LCMS (ESI) m/z: 433.0 $[M+H]^+$.

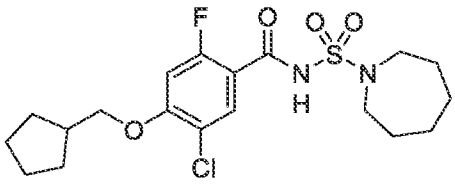
Example 226: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-(methylamino)azetidin-1-yl)sulfonyl)benzamide formate



(I)

[0555] Following the procedure described in **Example 31:** and making non-critical variations as required to replace *tert*-butyl 3-(azetidin-3-yloxy)pyrrolidine-1-carboxylate with *tert*-butyl azetidin-3-yl(methyl)carbamate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1 H), 7.77 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 12.4 Hz, 1H), 4.12 - 3.97 (m, 2H), 3.96 (d, J = 6.8 Hz, 2H), 3.84 - 3.76 (m, 1H), 3.75 - 3.69 (m, 2H), 2.52 (s, 3 H), 2.37 - 2.26 (m, 1H), 1.85 - 1.71 (m, 2H), 1.66 - 1.45 (m, 4H), 1.43 - 1.25 (m, 2H). LCMS (ESI) m/z: 420.1 $[M+H]^+$.

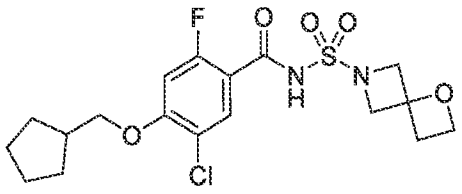
Example 227: *N*-(azepan-1-ylsulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

[0556] Following the procedure described in **Example 31:** and making non-critical variations as required to replace *tert*-butyl 3-(azetidin-3-yloxy)pyrrolidine-1-carboxylate with azepane, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 12.4 Hz, 1H), 4.02 (d, J = 6.8 Hz, 2H), 3.41 - 3.32 (m, 4H), 2.34 - 2.32 (m, 1H), 1.83 - 1.73 (m, 2H), 1.70 - 1.60 (m, 6H), 1.57 - 1.50 (m, 6H), 1.39 - 1.30 (m, 2H). LCMS (ESI) m/z: 433.0 $[M+H]^+$.

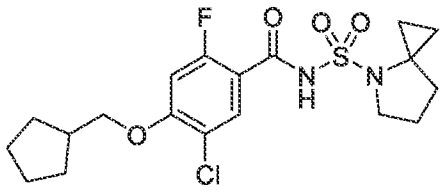
Example 228: *N*-((1-oxa-6-azaspiro[3.3]heptan-6-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

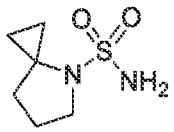
[0557] Following the procedure described in **Example 31** and making non-critical variations as required to replace *tert*-butyl 3-(azetidin-3-yloxy)pyrrolidine-1-carboxylate with 1-oxa-6-azaspiro[3.3]heptane, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (d, J = 8.0 Hz, 1H), 7.07 (s, 1H), 6.97 (d, J = 12.0 Hz, 1H), 4.36 (t, J = 7.6 Hz, 2H), 3.96 (d, J = 6.8 Hz, 2H), 3.85 (s, 4H), 2.76 (t, J = 7.2 Hz, 2H), 2.37 - 2.26 (m, 1H), 1.84 - 1.70 (m, 2H), 1.67 - 1.47 (m, 4H), 1.42 - 1.31 (m, 2H). LCMS (ESI) m/z: 433.0 $[M+H]^+$.

Example 229: *N*-((4-azaspiro[2.4]heptan-4-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide



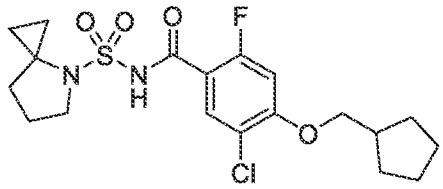
(I)

Step 1: 4-azaspiro[2.4]heptane-4-sulfonamide



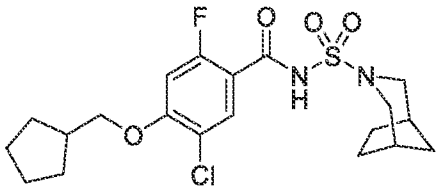
[0558] To a mixture of 4-azaspiro[2.4]heptane oxalate oxalic acid (100 mg, 0.53 mmol) in 1,4-dioxane (5 mL) was added sulfamide (130 mg, 1.34 mmol) and NEt_3 (162 mg, 1.60 mmol). The mixture was stirred at 110 °C for 16 h under nitrogen atmosphere. After cooling to room temperature, the reaction was diluted with water (50 mL) and extracted with EtOAc (50 mL x 2). The combined organic lawyers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (90 mg, crude) as a yellow oil that required no further purification.

Step 2: *N*-((4-azaspiro[2.4]heptan-4-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide



[0559] Following the procedure described in **Example 31** and making non-critical variations as required to replace *tert*-butyl 3-((1-sulfamoylazetidin-3-yl)oxy)pyrrolidine-1-carboxylate with 4-azaspiro[2.4]heptane-4-sulfonamide, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.90 (s, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.24 (d, *J* = 12.0 Hz, 1H), 4.03 (d, *J* = 6.8 Hz, 2H), 3.84 (t, *J* = 7.2 Hz, 2H), 2.38 - 2.28 (m, 1H), 1.95 - 1.85 (m, 2H), 1.83 - 1.73 (m, 2H), 1.72 - 1.67 (m, 2H), 1.66 - 1.50 (m, 4H), 1.41 - 1.29 (m, 2H), 1.25 - 1.18 (m, 2H), 0.65 - 0.59 (m, 2H). LCMS (ESI) m/z: 431.1 $[M+H]^+$.

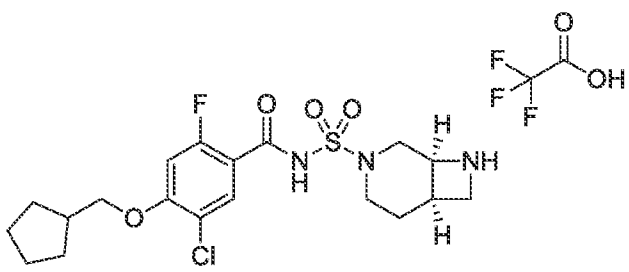
Example 230: *N*-(((1*R*,5*S*)-3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

[0560] Following the procedure described in **Example 31** and making non-critical variations as required to replace *tert*-butyl 3-(azetidin-3-yloxy)pyrrolidine-1-carboxylate with 4-azaspiro[2.4]heptane-4-sulfonamide, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.74 (s, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 12.4 Hz, 1H), 4.02 (d, *J* = 6.8 Hz, 2H), 3.47 - 3.43 (m, 2H), 3.01 (d, *J* = 11.2 Hz, 2H), 2.38 - 2.31 (m, 1H), 2.30 - 2.22 (m, 2H), 1.81 - 1.73 (m, 2H), 1.63 - 1.45 (m, 10H), 1.40 - 1.33 (m, 2H). LCMS (ESI) m/z: 445.2 $[M+H]^+$.

Example 231: *N*-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-ylsulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide 2,2,2-trifluoroacetate

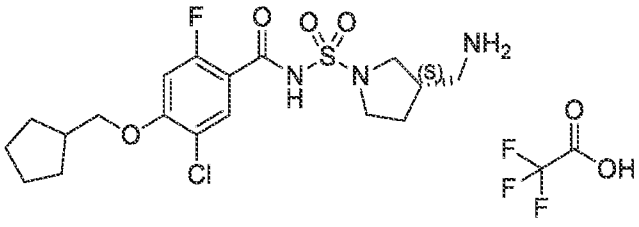


(I)

[0561] Following the procedure described in **Example 31**and making non-critical variations as required to replace *tert*-butyl 3-(azetidin-3-yloxy)pyrrolidine-1-carboxylate with *tert*-butyl

(1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (s, 1H), 8.90 (s, 1H), 7.74 (d, J = 7.2 Hz, 1H), 7.22 (d, J = 12.4 Hz, 1H), 4.64 - 4.52 (m, 1H), 4.09 - 3.93 (m, 3H), 3.80 - 3.73 (m, 1H), 3.68 - 3.52 (m, 4H), 3.31 - 3.19 (m, 1H), 2.90 - 2.83 (m, 1H), 2.38 - 2.28 (m, 1H), 2.05 - 1.96 (m, 1H), 1.86 - 1.71 (m, 3H), 1.67 - 1.48 (m, 4H), 1.41 - 1.29 (m, 2H). LCMS (ESI) m/z: 446.1 $[M+H]^+$.

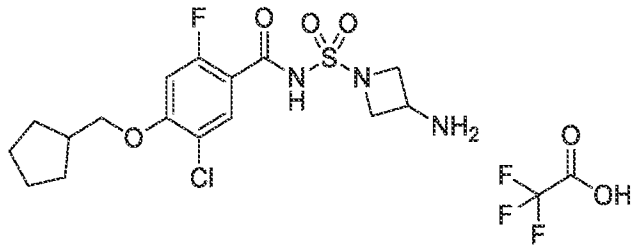
Example 232: (*S*)-*N*-((3-(aminomethyl)pyrrolidin-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide 2,2,2-trifluoroacetate



(I)

[0562] Following the procedure described in **Example 31** and making non-critical variations as required to replace *tert*-butyl 3-(azetidin-3-yloxy)pyrrolidine-1-carboxylate with *tert*-butyl (*R*)-(pyrrolidin-3-ylmethyl)carbamate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 7.79 (s, 2H), 7.73 (d, J = 7.2 Hz, 1H), 7.24 (d, J = 12.0 Hz, 1H), 4.03 (d, J = 6.8 Hz, 2H), 3.75 - 3.65 (m, 1H), 3.55 - 3.45 (m, 1H), 3.44 - 3.35 (m, 1H), 3.21 - 3.13 (m, 1H), 2.87 (s, 2H), 2.45 - 2.40 (m, 1H), 2.40 - 2.28 (m, 1H), 2.10 - 2.00 (m, 1H), 1.84 - 1.72 (m, 2H), 1.72 - 1.50 (m, 5H), 1.40 - 1.29 (m, 2H). LCMS (ESI) m/z: 434.0 $[M+H]^+$.

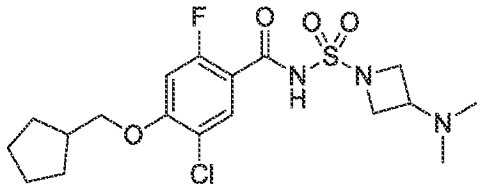
Example 233: N-((3-aminoazetidin-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

[0563] Following the procedure described in **Example 31** and making non-critical variations as required to replace *tert*-butyl 3-((1-sulfamoylazetidin-3-yl)oxy)pyrrolidine-1-carboxylate with *tert*-butyl (1-sulfamoylazetidin-3-yl)carbamate (reference: WO200624823), the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 2H), 7.77 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 12.4 Hz, 1H), 4.08 - 3.94 (m, 4H), 3.86 - 3.80 (m, 1H), 3.70 - 3.62 (m, 1H), 2.32 - 2.24 (m, 1H), 1.83 - 1.72 (m, 2H), 1.68 - 1.49 (m, 4H), 1.42 - 1.27 (m, 2H). LCMS (ESI) m/z: 406.1 $[M+H]^+$.

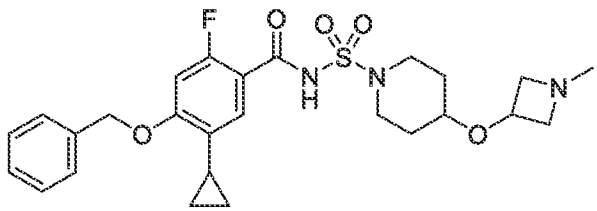
Example 234: 5-chloro-4-(cyclopentylmethoxy)-*N*-((3-(dimethylamino)azetidin-1-yl)sulfonyl)-2-fluorobenzamide



(I)

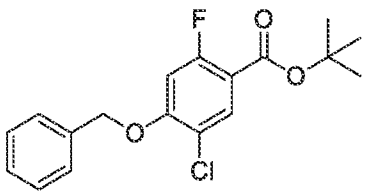
[0564] To a mixture of *N*-((4-(azetidin-3-yloxy)piperidin-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide (200 mg, 0.49 mmol, **Example 233**: in DCM (10 mL) was added formaldehyde (0.37 mL, 4.93 mmol, 37% in water) and $NaBH(OAc)_3$ (522 mg, 2.46 mmol). The resulting mixture was stirred at room temperature for 16 h. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) to pH > 7 and then extracted with EtOAc (50 mL x 2). The combined organic lawyers were washed with brine (60 mL), then dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by reverse phase chromatography (solvent gradient: acetonitrile 22 - 52% / (0.2% fomic acid) in water) to afford the title compound (28 mg, 13%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 12.4 Hz, 1H), 4.03 - 3.92 (m, 4H), 3.88 - 3.78 (m, 2H), 3.62 - 3.55 (m, 1H), 2.51 (s, 6H), 2.36 - 2.25 (m, 1H), 1.79 - 1.73 (m, 2H), 1.70 - 1.46 (m, 4H), 1.40 - 1.30 (m, 2H). LCMS (ESI) m/z: 434.2 $[M+H]^+$.

Example 236: 4-(benzyloxy)-5-cyclopropyl-2-fluoro-*N*-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide



(I)

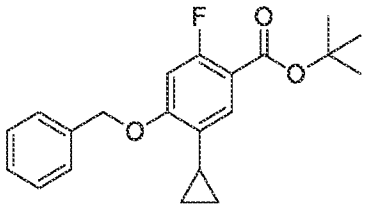
Step 1: *tert*-butyl 4-(benzyloxy)-5-chloro-2-fluorobenzoate



[0565] To a solution of *tert*-butyl 5-chloro-2,4-difluoro-benzoate (5.0 g, 20.11 mmol) and Cs_2CO_3 (13.1 g, 40.22 mmol) in DMSO (50 mL), benzyl alcohol (2.17 g, 20.11 mmol) was added. The reaction was stirred at 80 °C under nitrogen atmosphere for 16 h. After cooling to room temperature, the reaction was diluted with water (100 mL) and extracted with EtOAc (100 mL x

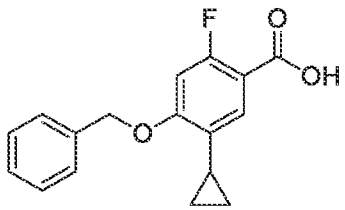
2). The combined organic lawyers were washed with brine (100 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 1% EtOAc in petroleum ether) to afford the title compound (4.7 g, 69%) as colorless oil. LCMS (ESI) m/z: 281.1 $[M-56+H]^+$.

Step 2: *tert*-butyl 4-(benzyloxy)-5-cyclopropyl-2-fluorobenzoate



[0566] To a solution of *tert*-butyl 4-benzyloxy-5-chloro-2-fluoro-benzoate (2.5 g, 7.42 mmol), K_3PO_4 (4.73 g, 22.27 mmol) and cyclopropylboronicacid (956 mg, 11.13 mmol) in toluene (17.5 mL) and water (2.5 mL), $Pd(OAc)_2$ (166 mg, 0.74 mmol) and 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (304 mg, 0.74 mmol) was added under nitrogen atmosphere at room temperature. The reaction was stirred at 100 °C for 16 h. After cooling to room temperature, the reaction was diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic lawyers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by silica gel chromatography (solvent gradient: 0 - 2% EtOAc in petroleum ether) to afford the title compound (2.1 g, 82%) as colorless oil. LCMS (ESI) m/z: 287.1 $[M-56+H]^+$.

Step 3: 4-(benzyloxy)-5-cyclopropyl-2-fluorobenzoic acid

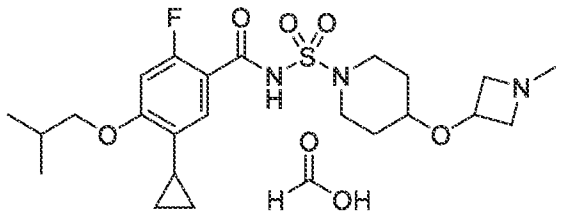


[0567] To a solution of *tert*-butyl 4-(benzyloxy)-5-cyclopropyl-2-fluorobenzoate (200 mg, 0.58 mmol) in DCM (2 mL) was added TFA (2 mL) under nitrogen atmosphere at room temperature. The reaction was stirred at room temperature for 2 h. The mixture was concentrated in vacuo to afford the title compound (160 mg, crude) as a white solid that required no further purification. LCMS (ESI) m/z: 287.2 $[M-56+H]^+$.

Step 4: 4-(benzyloxy)-5-cyclopropyl-2-fluoro-*N*-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide

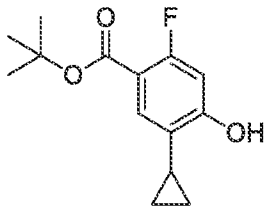
[0568] Following the procedure described in **Example 38** and making non-critical variations as required to replace *tert*-butyl 3-(piperidin-4-yloxy)pyrrolidine-1-carboxylate with *tert*-butyl 3-(piperidin-4-yloxy)azetidine-1-carboxylate (reference: *Tetrahedron Lett.*, **2007**, *48*, 791 - 794), 4-(benzyloxy)-5-chloro-2-fluorobenzoic acid with 4-(benzyloxy)-5-cyclopropyl-2-fluorobenzoic acid, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 7.50 - 7.43 (m, 2H), 7.42 - 7.35 (m, 2H), 7.33 - 7.28 (m, 1H), 7.22 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 12.8 Hz, 1H), 5.17 (s, 2H), 4.23 - 4.14 (m, 1H), 3.80 - 3.73 (m, 2H), 3.37 - 3.28 (m, 3H), 3.13 - 3.02 (m, 2H), 2.77 - 2.68 (m, 2H), 2.41 (s, 3H), 2.07 - 1.98 (m, 1H), 1.80 - 1.72 (m, 2H), 1.46 - 1.35 (m, 2H), 0.93 - 0.82 (m, 2H), 0.62 - 0.49 (m, 2H). LCMS (ESI) m/z: 518.3 $[M+H]^+$.

Example 237: 5-cyclopropyl-2-fluoro-4-isobutoxy-*N*-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide formic acid



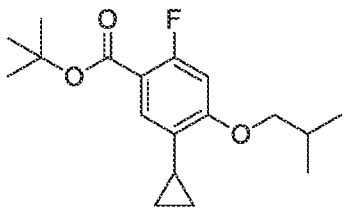
(I)

Step 1: *tert*-butyl 5-cyclopropyl-2-fluoro-4-hydroxybenzoate



[0569] To a solution of *tert*-butyl 4-(benzyloxy)-5-cyclopropyl-2-fluorobenzoate (1.4 g, 4.09 mmol) in ethanol (30 mL) and Pd/C (870 mg, 0.82 mmol) was added at room temperature. The mixture was stirred at room temperature under hydrogen atmosphere (15 psi) for 16 h. The reaction was filtered and concentrated in vacuo to afford the title compound (1.0 g, crude) as colorless oil that required no further purification. LCMS (ESI) m/z: 197.1 $[M-56+H]^+$.

Step 2: *tert*-butyl 5-cyclopropyl-2-fluoro-4-isobutoxybenzoate



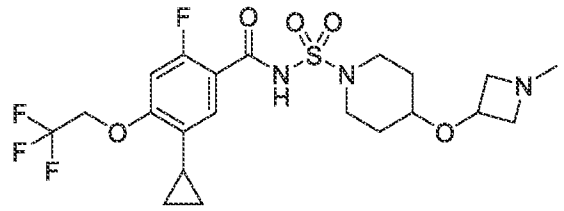
[0570] To a stirred solution of *tert*-butyl 5-cyclopropyl-2-fluoro-4-hydroxybenzoate (250 mg, 0.10 mmol) in DMF (5 mL) was added K_2CO_3 (1.1 g, 7.9 mmol) and 1-iodo-2-methylpropane

(912 mg, 4.95 mmol) at room temperature under nitrogen atmosphere. Then the reaction was stirred at 70 °C for 16 h. After cooling to room temperature, the reaction was diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL x 4), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the title compound (300 mg, 98%) as yellow oil that required no further purification. LCMS (ESI) m/z: 253.1 $[M-56+H]^+$.

Step 3: 5-cyclopropyl-2-fluoro-4-isobutoxy-*N*-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide formic acid

[0571] Following the procedure described in **Example 236** and making non-critical variations as required to replace *tert*-butyl 4-(benzyloxy)-5-cyclopropyl-2-fluorobenzoate with *tert*-butyl 5-cyclopropyl-2-fluoro-4-isobutoxybenzoate, *tert*-butyl 4-(benzyloxy)-5-cyclopropyl-2-fluorobenzoate with *tert*-butyl 5-cyclopropyl-2-fluoro-4-isobutoxybenzoate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.16 (d, J = 8.8 Hz, 1H), 6.72 (d, J = 12.8 Hz, 1H), 4.36 - 4.26 (m, 1H), 4.09 - 4.00 (m, 2H), 3.80 (d, J = 6.4 Hz, 2H), 3.58 - 3.50 (m, 1H), 3.44 - 3.36 (m, 4H), 2.88 - 2.78 (m, 2H), 2.65 (s, 3H), 2.09 - 1.96 (m, 2H), 1.84 - 1.75 (m, 2H), 1.48 - 1.39 (m, 2H), 1.01 (d, J = 6.8 Hz, 6H), 0.90 - 0.82 (m, 2H), 0.60 - 0.53 (m, 2H). LCMS (ESI) m/z: 484.2 $[M+H]^+$.

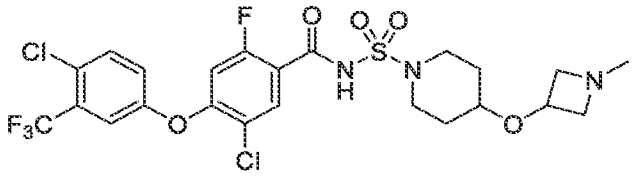
Example 238: 5-cyclopropyl-2-fluoro-*N*-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)-4-(2,2,2-trifluoroethoxy)benzamide



(I)

[0572] Following the procedure described in **Example 237** and making non-critical variations as required to replace 1-iodo-2-methylpropane with 1,1,1-trifluoro-2-iodoethane, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.20 (d, J = 8.4 Hz, 1 H), 6.91 (d, J = 12.0 Hz, 1 H), 4.83 (q, J = 8.8 Hz, 2H), 4.42 - 4.30 (m, 1H), 4.18 - 4.10 (m, 2H), 3.72 - 3.57 (m, 5H), 2.83 - 2.76 (m, 2H), 2.70 (s, 3H), 2.03 - 1.93 (m, 1H), 1.86 - 1.76 (m, 2H), 1.51 - 1.36 (m, 2H), 0.97 - 0.83 (m, 2H), 0.65 - 0.55 (m, 2H). LCMS (ESI) m/z: 510.1 $[M+H]^+$.

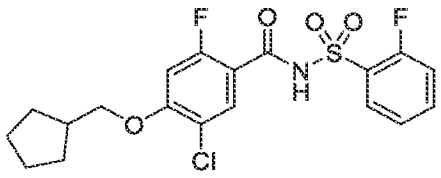
Example 239: 5-chloro-4-(4-chloro-3-(trifluoromethyl)phenoxy)-2-fluoro-*N*-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide



(I)

[0573] Following the procedure described in **Example 237** and making non-critical variations as required to replace *tert*-butyl 5-cyclopropyl-2-fluoro-4-isobutoxybenzoate with *tert*-butyl 5-chloro-4-(4-chloro-3-(trifluoromethyl)phenoxy)-2-fluorobenzoate, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, J = 7.2 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 3.2 Hz, 1H), 7.34 - 7.27 (m, 1H), 7.13 (d, J = 10.4 Hz, 1H), 4.45 - 4.37 (m, 1H), 4.28 - 4.21 (m, 2H), 3.89 - 3.79 (m, 2H), 3.45 - 3.40 (m, 2H), 2.79 (s, 3H), 2.78 - 2.65 (m, 3H), 1.85 - 1.78 (m, 2H), 1.46 - 1.37 (m, 2H). LCMS (ESI) m/z: 600.1 $[M+H]^+$.

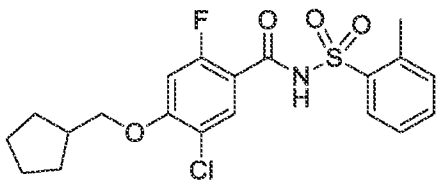
Example 241: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-fluorophenyl)sulfonyl)benzamide



(I)

[0574] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(3-(dimethylamino)piperidin-1-yl)-2-fluorobenzenesulfonamide with 2-fluorobenzenesulfonamide, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 - 7.94 (m, 1H), 7.84 - 7.74 (m, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.51 - 7.40 (m, 2H), 7.20 (d, J =12.4 Hz, 1H), 4.01 (d, J =7.2 Hz, 2H), 2.38 - 2.25 (m, 1H), 1.78 - 1.70 (m, 2H), 1.62 - 1.45 (m, 4H), 1.38 - 1.30 (m, 2H). LCMS (ESI) m/z: 430.1 $[M+H]^+$.

Example 242: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(o-tolylsulfonyl)benzamide

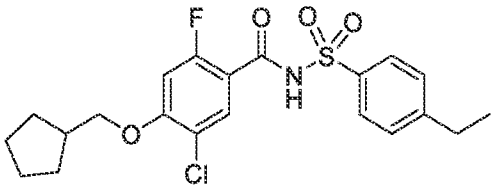


(I)

[0575] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(3-(dimethylamino)piperidin-1-yl)-2-fluorobenzenesulfonamide with 1 2-fluorobenzenesulfonamide, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.64 (s, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.63 - 7.56 (m, 1H),

7.49 - 7.41 (m, 2H), 7.22 (d, *J* = 12.4 Hz, 1H), 4.01 (d, *J* = 6.8 Hz, 2H), 2.61 (s, 3H), 2.38 - 2.25 (m, 1H), 1.82 - 1.70 (m, 2H), 1.67 - 1.47 (m, 4H), 1.40 - 1.29 (m, 2H). LCMS (ESI) m/z: 426.0 $[M+H]^+$.

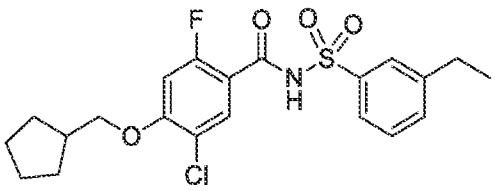
Example 243: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-ethylphenyl)sulfonyl)-2-fluorobenzamide



(I)

[0576] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(3-(dimethylamino)piperidin-1-yl)-2-fluorobenzenesulfonamide with 4-ethylbenzenesulfonamide, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.41 (s, 1H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 12.4 Hz, 1H), 4.01 (d, *J* = 7.2 Hz, 2H), 2.75 - 2.65 (m, 2H), 2.40 - 2.25 (m, 1H), 1.82 - 1.69 (m, 2H), 1.66 - 1.47 (m, 4H), 1.41 - 1.26 (m, 2H), 1.21 (t, *J* = 7.6 Hz, 3H). LCMS (ESI) m/z: 440.2 $[M+H]^+$.

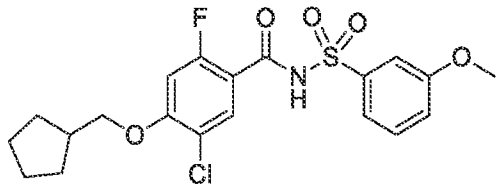
Example 244: 5-chloro-4-(cyclopentylmethoxy)-*N*-((3-ethylphenyl)sulfonyl)-2-fluorobenzamide



(I)

[0577] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(3-(dimethylamino)piperidin-1-yl)-2-fluorobenzenesulfonamide with 3-ethylbenzenesulfonamide, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (s, 1H), 7.83 - 7.77 (m, 2H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.62 - 7.52 (m, 2H), 7.22 (d, *J* = 12.4 Hz, 1H), 4.01 (d, *J* = 6.8 Hz, 2H), 2.72 (q, *J* = 7.2 Hz, 2H), 2.40 - 2.28 (m, 1H), 1.82 - 1.69 (m, 2H), 1.66 - 1.47 (m, 4H), 1.39 - 1.23 (m, 2H), 1.21 (t, *J* = 7.2 Hz, 3H). LCMS (ESI) m/z: 440.0 $[M+H]^+$.

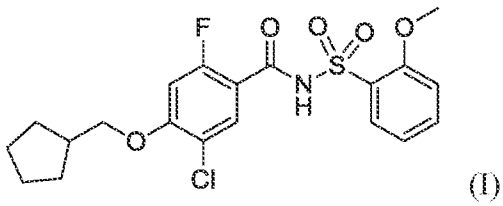
Example 245: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-methoxyphenyl)sulfonyl)benzamide



(I)

[0578] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(3-(dimethylamino)piperidin-1-yl)-2-fluorobenzenesulfonamide with 3-methoxybenzenesulfonamide, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (s, 1H), 7.69 (d, J = 7.62 Hz, 1H), 7.65 - 7.53 (m, 2H), 7.45 (s, 1H), 7.30 - 7.23 (m, 1H), 7.22 (d, J = 12.8 Hz, 1H), 4.02 (d, J = 6.8 Hz, 2H), 3.84 (s, 3H), 2.35 - 2.27 (m, 1H), 1.81 - 1.70 (m, 2H), 1.68 - 1.46 (m, 4H), 1.39 - 1.28 (m, 2H). LCMS (ESI) m/z: 442.1 $[M+H]^+$.

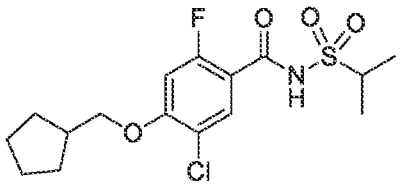
Example 246: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methoxyphenyl)sulfonyl)benzamide



(I)

[0579] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(3-(dimethylamino)piperidin-1-yl)-2-fluorobenzenesulfonamide with 2-methoxybenzenesulfonamide, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.72 - 7.61 (m, 2H), 7.26 (d, J = 8.4 Hz, 1H), 7.22 - 7.08 (m, 2H), 4.01 (d, J = 6.8 Hz, 2H), 3.90 (s, 3H), 2.40 - 2.28 (m, 1H), 1.82 - 1.70 (m, 2H), 1.67 - 1.46 (m, 4H), 1.40 - 1.27 (m, 2H). LCMS (ESI) m/z: 442.1 $[M+H]^+$.

Example 247: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(isopropylsulfonyl)benzamide

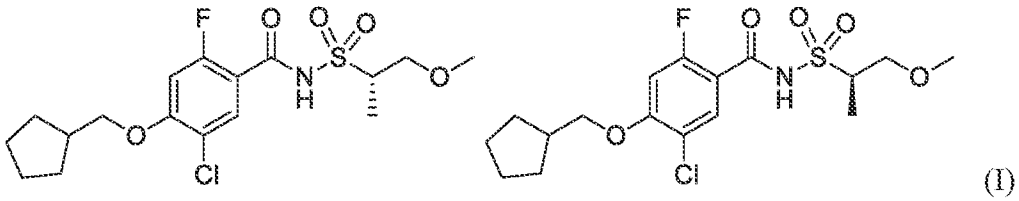


(I)

[0580] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(3-(dimethylamino)piperidin-1-yl)-2-fluorobenzenesulfonamide with

propane-2-sulfonamide, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.25 (d, J = 12.4 Hz, 1H), 4.03 (d, J = 6.8 Hz, 2H), 3.85 - 3.75 (m, 1H), 2.38 - 2.27 (m, 1H), 1.82 - 1.71 (m, 2H), 1.67 - 1.48 (m, 4H), 1.41 - 1.33 (m, 2H), 1.31 (d, J = 6.8 Hz, 6H). LCMS (ESI) m/z: 378.1 $[M+H]^+$.

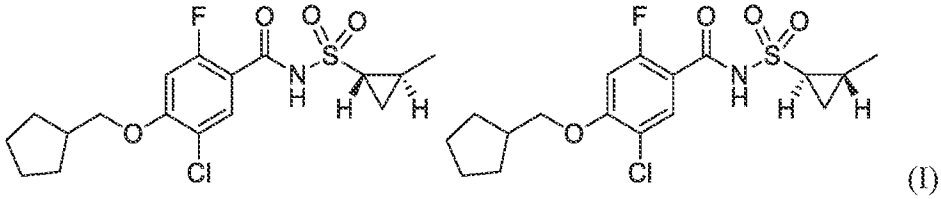
Example 248 and Example 249: (*S*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((1-methoxypropan-2-yl)sulfonyl)benzamide, and (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((1-methoxypropan-2-yl)sulfonyl)-benzamide



(I)

[0581] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(3-(dimethylamino)piperidin-1-yl)-2-fluorobenzenesulfonamide with 1-methoxypropane-2-sulfonamide, 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((1-methoxypropan-2-yl)sulfonyl)benzamide was obtained as a yellow solid. 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((1-methoxypropan-2-yl)sulfonyl)benzamide (150 mg, 0.37 mmol) was separated by using chiral SFC (DAICEL CHIRALPAK AY-H (250 mm * 30 mm, 5 um), Supercritical CO_2 / EtOH + 0.1% NH_3•H_2O = 40/60; 60 mL/min) to afford (*S*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((1-methoxypropan-2-yl)sulfonyl)benzamide (19 mg, second peak) as a yellow solid and (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((1-methoxypropan-2-yl)sulfonyl)benzamide (30 mg, first peak) as a yellow solid. Absolute configuration was arbitrarily assigned to each enantiomer. **Example 248:**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 12.4 Hz, 1H), 4.02 (d, J = 6.8 Hz, 2H), 3.92 - 3.80 (m, 1H), 3.75 - 3.65 (m, 1H), 3.58 - 3.47 (m, 1H), 3.23 (s, 3H), 2.40 - 2.27 (m, 1H), 1.83 - 1.70 (m, 2H), 1.66 - 1.48 (m, 4H), 1.41 - 1.33 (m, 2H), 1.31 (d, J = 6.8 Hz, 3H). LCMS (ESI) m/z: 408.2 $[M+H]^+$. **Example 249:**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (s, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 12.4 Hz, 1H), 4.02 (d, J = 6.8 Hz, 2H), 3.92 - 3.80 (m, 1H), 3.75 - 3.65 (m, 1H), 3.58 - 3.47 (m, 1H), 3.23 (s, 3H), 2.40 - 2.27 (m, 1H), 1.83 - 1.70 (m, 2H), 1.66 - 1.48 (m, 4H), 1.41 - 1.33 (m, 2H), 1.31 (d, J = 6.8 Hz, 3H). LCMS (ESI) m/z: 408.1$[M+H]^+$.

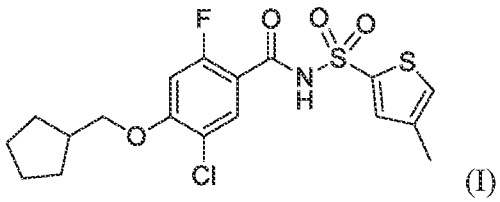
Example 250 and Example 251: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(((1*S*,2*S*)-2-methylcyclopropyl)sulfonyl)benzamide, and 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(((1*R*,2*R*)-2-methylcyclopropyl)sulfonyl)-benzamide



(I)

[0582] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(3-(dimethylamino)piperidin-1-yl)-2-fluorobenzenesulfonamide with (1*S*,2*S*)-2-methylcyclopropane-1-sulfonamide, 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((*trans*-2-methylcyclopropyl)sulfonyl)benzamide was obtained as a white solid. 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((*trans*-2-methylcyclopropyl)sulfonyl)benzamide (240 mg, 0.62 mmol) was separated by using chiral SFC (DAICEL CHIRALPAK IC (250 mm * 30 mm, 10 um), Supercritical CO_2 / EtOH + 0.1% $NH_3 \cdot H_2O$ = 70/30; 70 mL/min) to afford 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(((1*S*,2*S*)-2-methylcyclopropyl)sulfonyl)benzamide (65 mg, first peak) as a white solid and 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(((1*R*,2*R*)-2-methylcyclopropyl)sulfonyl)benzamide (72 mg, second peak) as a white solid. Absolute configuration was arbitrarily assigned to each enantiomer. **Example 250:** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 12.8 Hz, 1H), 4.04 (d, J = 6.8 Hz, 2H), 2.85 - 2.75 (m, 1H), 2.40 - 2.28 (m, 1H), 1.83 - 1.69 (m, 2H), 1.67 - 1.48 (m, 5H), 1.41 - 1.23 (m, 3H), 1.10 (d, J = 6.0 Hz, 3H), 1.03 - 0.91 (m, 1H). LCMS (ESI) m/z: 390.0 $[M+H]^+$. **Example 251:** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 12.8 Hz, 1H), 4.03 (d, J = 6.8 Hz, 2H), 2.85 - 2.75 (m, 1H), 2.40 - 2.28 (m, 1H), 1.85 - 1.68 (m, 2H), 1.68 - 1.45 (m, 5H), 1.42 - 1.22 (m, 3H), 1.10 (d, J = 6.0 Hz, 3H), 1.03 - 0.91 (m, 1H). LCMS (ESI) m/z: 390.0 $[M+H]^+$.

Example 252: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-methylthiophen-2-yl)sulfonyl)benzamide

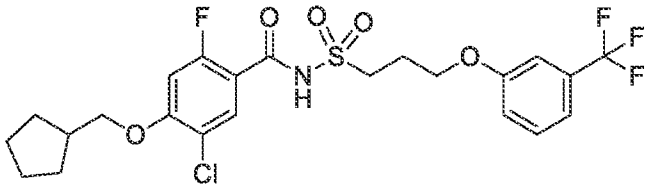


(I)

[0583] To a solution of NaH (41 mg, 1.02 mmol, 60% in mineral oil) in DMF (2 mL) was added 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide (332 mg, 1.22 mmol) at 0 °C under nitrogen atmosphere. After stirring at 0 °C for 10 min, 4-methylthiophene-2-sulfonyl chloride

(200 mg, 1.02 mmol) in DMF (2 mL) was added at 0 °C. After stirring at room temperature for 16 h, the reaction was quenched with water (30 mL) and extracted with EtOAc (60 mL x 3). The combined organic lawyers were washed with brine (30 mL x 5), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by reverse phase chromatography (acetonitrile 65 - 95% / 0.2% formic acid in water) to afford the title compound (164 mg, 37%) as a white soild. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.61 (s, 1H), 7.76 - 7.62 (m, 3H), 7.23 (d, J = 12.4 Hz, 1H), 4.02 (d, J = 6.8 Hz, 2H), 2.37 - 2.28 (m, 1H), 2.25 (s, 3H), 1.82 - 1.72 (m, 2H), 1.67 - 1.48 (m, 4H), 1.38 - 1.29 (m, 2H). LCMS (ESI) m/z: 431.9 $[M+H]^+$.

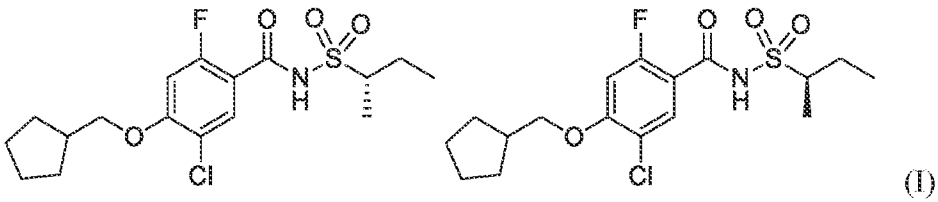
Example 253: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((3-(3-(trifluoromethyl)phenoxy)propyl)sulfonyl)benzamide



(I)

[0584] Following the procedure described in **Example 252** and making non-critical variations as required to replace 4-methylthiophene-2-sulfonyl chloride with 3-(3-(trifluoromethyl)-phenoxy)propane-1-sulfonyl chloride, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.08 (s, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.52 - 7.46 (m, 1H), 7.31 - 7.16 (m, 4H), 4.19 (t, J = 6.0 Hz, 2H), 4.02 (d, J = 6.8 Hz, 2H), 3.75 - 3.65 (m, 2H), 2.45 - 2.35 (m, 1H), 2.25 - 2.13 (m, 2H), 1.85 - 1.75 (m, 2H), 1.68 - 1.48 (m, 4H), 1.42 - 1.29 (m, 2H). LCMS (ESI) m/z: 538.1 [M+H]+.

Example 254 and Example 255: (*S*)-*N*-(*sec*-butylsulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide, and (*R*)-*N*-(*sec*-butylsulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide

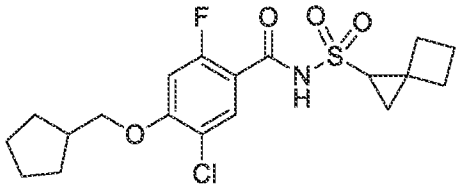


(I)

[0585] Following the procedure described in **Example 252** and making non-critical variations as required to replace 4-methylthiophene-2-sulfonyl chloride with (1*S*,2*S*)-2-methylcyclopropane-1-sulfonamide, *N*-(*sec*-butylsulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide was obtained as a white solid. *N*-(*sec*-butylsulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide (120 mg, 0.31 mmol) was separated by using chiral SFC (DAICEL CHIRALCEL OD-H (250 mm * 30 mm, 5 um), Supercritical CO_2 / MeOH + 0.1% NH_3•H_2O =

20/80; 60 mL/min) to afford (*S*)-*N*-(*sec*-butylsulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide (50 mg, second peak) as a white solid and (*R*)-*N*-(*sec*-butylsulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide (50 mg, first peak) as a white solid. Absolute configuration was arbitrarily assigned to each enantiomer. **Example 254:** ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 7.73 (d, J = 7.2 Hz, 1H), 7.23 (d, J = 12.0 Hz, 1H), 4.03 (d, J = 6.8 Hz, 2H), 3.58 - 3.46 (m, 1H), 2.38 - 2.27 (m, 1H), 2.02 - 1.89 (m, 1H), 1.83 - 1.72 (m, 2H), 1.64 - 1.48 (m, 5H), 1.39 - 1.30 (m, 2H), 1.30 (d, J = 7.2 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H). LCMS (ESI) m/z: 392.1 $[M+H]^+$. **Example 255:** ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 1H), 7.73 (d, J = 7.2 Hz, 1H), 7.21 (d, J = 12.0 Hz, 1H), 4.03 (d, J = 6.8 Hz, 2H), 3.59 - 3.47 (m, 1H), 2.40 - 2.29 (m, 1H), 1.99 - 1.89 (m, 1H), 1.83 - 1.72 (m, 2H), 1.67 - 1.47 (m, 5H), 1.41 - 1.32 (m, 2H), 1.29 (d, J = 6.8 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H). LCMS (ESI) m/z: 392.2 $[M+H]^+$.

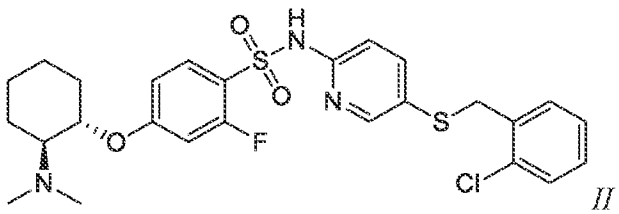
Example 256: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(spiro[2.3]hexan-1-ylsulfonyl)benzamide



(I)

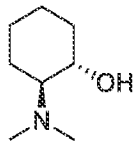
[0586] Following the procedure described in **Example 252** and making non-critical variations as required to replace 4-methylthiophene-2-sulfonyl chloride with spiro[2.3]hexane-1-sulfonyl chloride, the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.25 (d, J = 12.0 Hz, 1H), 4.04 (d, J = 6.8 Hz, 2H), 3.02 - 2.93 (m, 1H), 2.64 - 2.55 (m, 1H), 2.42 - 2.26 (m, 1H), 2.26 - 2.20 (m, 1H), 2.19 - 2.10 (m, 1H), 2.08 - 2.00 (m, 2H), 1.98 - 1.89 (m, 1H), 1.82 - 1.72 (m, 2H), 1.66 - 1.48 (m, 4H), 1.39 - 1.28 (m, 4H). LCMS (ESI) m/z: 416.2 $[M+H]^+$.

Example 257: *N*-(5-((2-chlorobenzyl)thio)pyridin-2-yl)-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzenesulfonamide



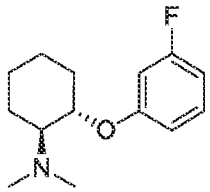
II

Step 1: (1*S*,2*S*)-2-(dimethylamino)cyclohexanol



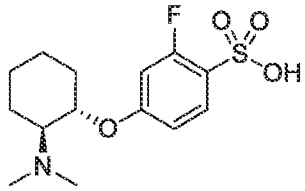
[0587] To a solution of (1*S*,2*S*)-2-aminocyclohexanol (5.0 g, 43.41 mmol) in formic acid (16 mL, 433 mmol) was added formaldehyde (32 mL, 433 mmol, 37% in water). The reaction mixture was stirred at 110 °C for 3 h. After cooling to room temperature, the mixture was concentrated in vacuo. The residue was dissolved in EtOAc (50 mL) and basified to pH = 13 by anhydrous NaOH (5 M). The aqueous phase was extracted with EtOAc (75 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give the title compound (7.8 g, crude) as yellow oil that required no further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 1H), 3.37 - 3.24 (m, 1H), 2.23 (s, 6H), 2.18 - 2.09 (m, 1H), 2.08 - 2.03 (m, 1H), 1.81 - 1.61 (m, 3H), 1.24 - 1.11 (m, 4H).

Step 2: (1*S*,2*S*)-2-(3-fluorophenoxy)-*N*,*N*-dimethylcyclohexanamine



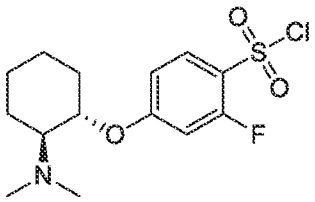
[0588] To a stirred solution of NaH (600.0 mg, 15.00 mmol, 60% in mineral oil) in 1-methyl-2-pyrrolidinone (20 mL) was added (1*S*,2*S*)-2-(dimethylamino)cyclohexanol (2.0 g, 13.96 mmol) slowly at 0 °C. The mixture was stirred at room temperature for 20 min and then 1,3-difluorobenzene (1.91 g, 16.76 mmol) was added. The reaction was stirred at 100 °C for an additional 2 h. After cooling to room temperature, the mixture was quenched with brine (50 mL) and extracted by EtOAc (100 mL). The organic layer was washed with brine (100 mL x 5), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give the title compound (1.9 g, crude) as yellow oil that required no further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 - 7.16 (m, 1H), 6.78 - 6.68 (m, 1H), 6.67 - 6.57 (m, 2H), 4.31 - 4.18 (m, 1H), 2.72 - 2.68 (m, 1H), 2.45 (s, 6H), 2.21 - 2.18 (m, 1H), 1.96 - 1.85 (m, 1H), 1.83 - 1.70 (m, 2H), 1.36 - 1.25 (m, 4H). LCMS M/Z (M+H) 238.2.

Step 3: 4-(((1*S*, 2*S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzenesulfonic acid



[0589] To a solution of (1*S*,2*S*)-2-(3-fluorophenoxy)-*N*,*N*-dimethyl-cyclohexanamine (3.0 g, 12.64 mmol) in anhydrous DCM (60 mL) was added chlorosulfonic acid (2.18 mL, 31.60 mmol) at 0 °C slowly. The mixture was stirred at 0 °C for 3 h under a nitrogen atmosphere. The reaction was quenched by water (30 mL). The aqueous phase was neutralized by 28% ammonium hydroxide to pH = 9 and then the mixture was concentrated in vacuo to remove most organic solvent. The residue was purified by reverse phase chromatography (acetonitrile 0 - 30% / 0.05% NH_4OH in water) to give the title compound (803 mg, 20%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.58 (dd, J = 8.8, 8.8 Hz, 1H), 6.88 (dd, J = 11.6, 2.4 Hz, 1H), 6.80 (dd, J = 8.8, 2.4 Hz, 1H), 4.70 - 4.59 (m, 1H), 3.49 - 3.47 (m, 1H), 2.71 (s, 6H), 2.20 - 2.12 (m, 1H), 2.07 - 2.00 (m, 1H), 1.82 - 1.75 (m, 1H), 1.70 - 1.60 (m, 1H), 1.54 - 1.36 (m, 2H), 1.35 - 1.25 (m, 2H). LCMS M/Z (M+H) 318.2.

Step 4: 4-(((1S,2S)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzene-1-sulfonyl chloride



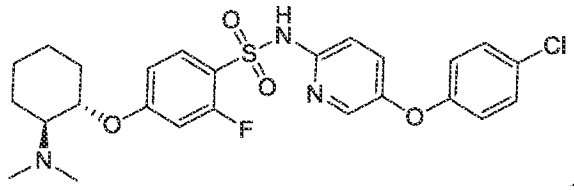
[0590] To a solution of 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzenesulfonic acid (48 mg, 0.15 mmol) in DCM (2.5 mL) was added $SOCl_2$ (179 mg, 1.5 mmol) and two drops of DMF at 0 °C. The mixture was stirred at room temperature for 2 h. The reaction was concentrated in vacuo to afford the title compound (40 mg, crude) as colorless oil that required no further purification. LCMS (ESI) m/z: 336.0 $[M+H]^+$.

Step 5: *N*-(5-((2-chlorobenzyl)thio)pyridin-2-yl)-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzenesulfonamide

[0591] To a solution of 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzene-1-sulfonyl chloride (40 mg, 0.13) and 5-((2-chlorobenzyl)thio)pyridin-2-amine (25 mg, 0.10 mmol) in pyridine (1 mL) was added 4A MS under a nitrogen atmosphere. The mixture was stirred at 80 °C for 5 h. The mixture was concentrated in vacuo and the crude residue was purified by

reverse phase chromatography (acetonitrile 30 - 70% / 0.2% HCOOH in water) to afford the title compound (14 mg, 44%). LCMS (ESI) m/z: 550.1 $[M+H]^+$.

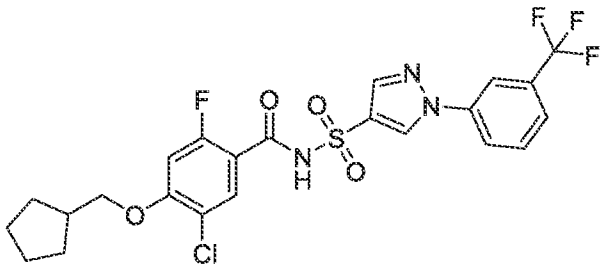
Example 258: *N*-(5-(4-chlorophenoxy)pyridin-2-yl)-4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzenesulfonamide



II

[0592] Following the procedure described in **Example 257** and making non-critical variations as required to replace 5-((2-chlorobenzyl)thio)pyridin-2-amine with 5-(4-chlorophenoxy)pyridin-2-amine. The title compound was obtained. LCMS (ESI) m/z: 520.1 $[M+H]^+$.

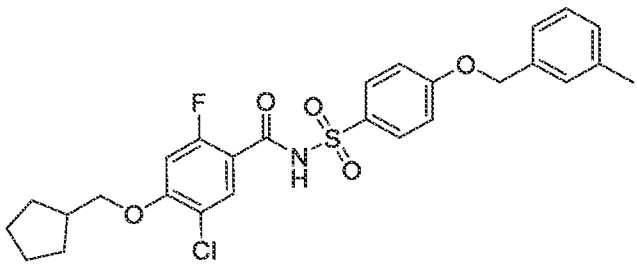
Example 259: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((1-(3-(trifluoromethyl)phenyl)-1*H*-pyrazol-4-yl)sulfonyl)benzamide



(I)

[0593] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with 1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-4-sulfonamide. The title compound was obtained. LCMS (ESI) m/z: 546.1 $[M+H]^+$.

Example 260: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((3-methylbenzyl)oxy)phenyl)sulfonyl)benzamide

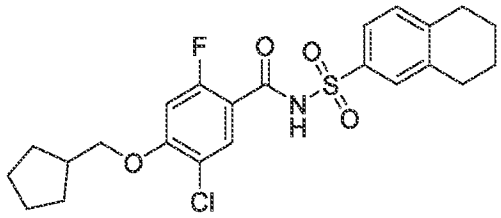


(I)

[0594] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-

difluorobenzenesulfonamide with 4-((3-methylbenzyl)oxy)benzenesulfonamide. The title compound was obtained. LCMS (ESI) m/z: 532.1 $[M+H]^+$.

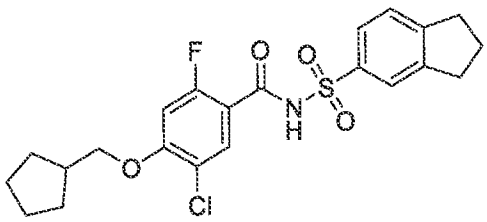
Example 261: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((5,6,7,8-tetrahydronaphthalen-2-yl)sulfonyl)benzamide



(I)

[0595] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with 5,6,7,8-tetrahydronaphthalene-2-sulfonamide. The title compound was obtained. LCMS (ESI) m/z: 466.1 $[M+H]^+$.

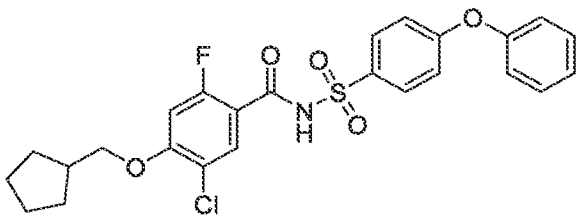
Example 262: 5-chloro-4-(cyclopentylmethoxy)-*N*-((2,3-dihydro-1*H*-inden-5-yl)sulfonyl)-2-fluorobenzamide



(I)

[0596] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with 2,3-dihydro-1*H*-indene-5-sulfonamide. The title compound was obtained. LCMS (ESI) m/z: 452.1 $[M+H]^+$.

Example 263: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-phenoxyphenyl)sulfonyl)benzamide

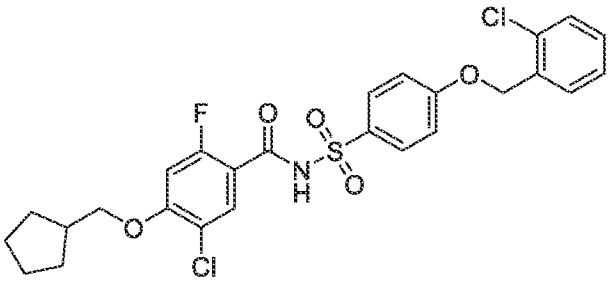


(I)

[0597] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-

difluorobenzenesulfonamide with 4-phenoxybenzenesulfonamide. The title compound was obtained. LCMS (ESI) m/z: 504.1 $[M+H]^+$.

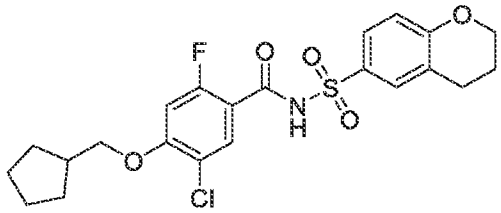
Example 264: 5-chloro-*N*-((4-((2-chlorobenzyl)oxy)phenyl)sulfonyl)-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

[0598] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzene-sulfonamide with 4-((2-chlorobenzyl)oxy)benzenesulfonamide. The title compound was obtained. LCMS (ESI) m/z: 552.1 $[M+H]^+$.

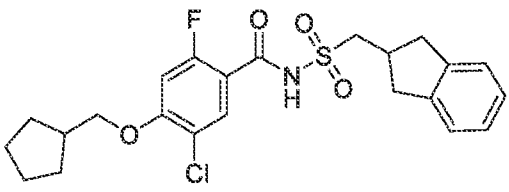
Example 265: 5-chloro-*N*-(chroman-6-ylsulfonyl)-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

[0599] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with chroman-6-sulfonamide. The title compound was obtained. LCMS (ESI) m/z: 468.1 $[M+H]^+$.

Example 266: 5-chloro-4-(cyclopentylmethoxy)-*N*-(((2,3-dihydro-1*H*-inden-2-yl)methyl)sulfonyl)-2-fluorobenzamide

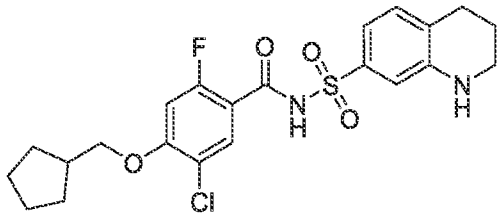


(I)

[0600] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-

difluorobenzenesulfonamide with (2,3-dihydro-1*H*-inden-2-yl)methanesulfonamide. The title compound was obtained. LCMS (ESI) m/z: 466.1 $[M+H]^+$.

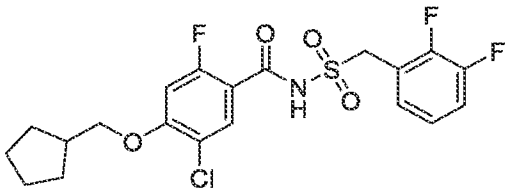
Example 267: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((1,2,3,4-tetrahydroquinolin-7-yl)sulfonyl)benzamide



(I)

[0601] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with 1,2,3,4-tetrahydroquinoline-7-sulfonamide. The title compound was obtained. LCMS (ESI) m/z: 467.1 $[M+H]^+$.

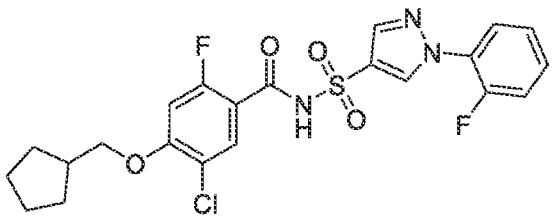
Example 268: 5-chloro-4-(cyclopentylmethoxy)-*N*-((2,3-difluorobenzyl)sulfonyl)-2-fluorobenzamide



(I)

[0602] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with (2,3-difluorophenyl)methanesulfonamide. The title compound was obtained. LCMS (ESI) m/z: 462.0 $[M+H]^+$.

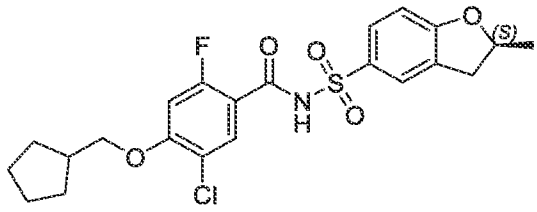
Example 269: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((1-(2-fluorophenyl)-1*H*-pyrazol-4-yl)sulfonyl)benzamide



(I)

[0603] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with 1-(2-fluorophenyl)-1*H*-pyrazole-4-sulfonamide. The title compound was obtained. LCMS (ESI) m/z: 496.1 $[M+H]^+$.

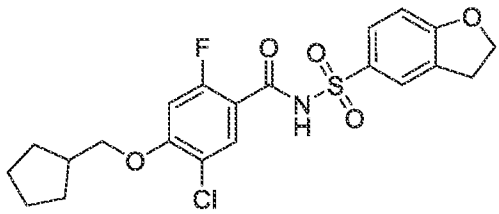
Example 270: (*S*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((2-methyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)benzamide



(I)

[0604] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with (*S*)-2-methyl-2,3-dihydrobenzofuran-5-sulfonamide. The title compound was obtained. LCMS (ESI) m/z: 468.1 $[M+H]^+$.

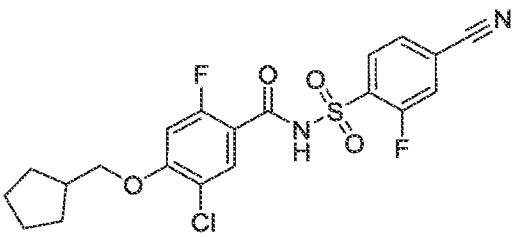
Example 271: 5-chloro-4-(cyclopentylmethoxy)-*N*-((2,3-dihydrobenzofuran-5-yl)sulfonyl)-2-fluorobenzamide



(I)

[0605] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with 2,3-dihydrobenzofuran-5-sulfonamide. The title compound was obtained. LCMS (ESI) m/z: 454.1 $[M+H]^+$.

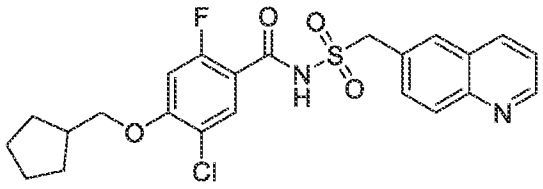
Example 272: 5-chloro-*N*-((4-cyano-2-fluorophenyl)sulfonyl)-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

[0606] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with 4-cyano-2-fluorobenzenesulfonamide. The title compound was obtained. LCMS (ESI) m/z: 455.0 $[M+H]^+$.

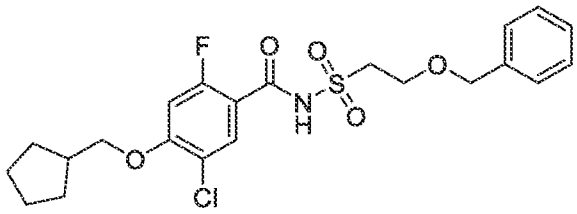
Example 273: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((quinolin-6-ylmethyl)sulfonyl)benzamide



(I)

[0607] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with quinolin-6-ylmethanesulfonamide. The title compound was obtained. LCMS (ESI) m/z: 477.1 $[M+H]^+$.

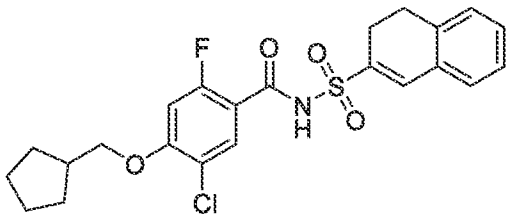
Example 274: *N*-((2-(benzyloxy)ethyl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

[0608] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with 2-(benzyloxy)ethanesulfonamide. The title compound was obtained. LCMS (ESI) m/z: 470.2 $[M+H]^+$.

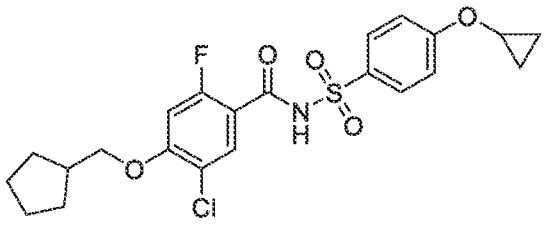
Example 275: 5-chloro-4-(cyclopentylmethoxy)-*N*-((3,4-dihydronaphthalen-2-yl)sulfonyl)-2-fluorobenzamide



(I)

[0609] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzene-sulfonamide with 3,4-dihydronaphthalene-2-sulfonamide. The title compound was obtained. LCMS (ESI) m/z: 464.2 $[M+H]^+$.

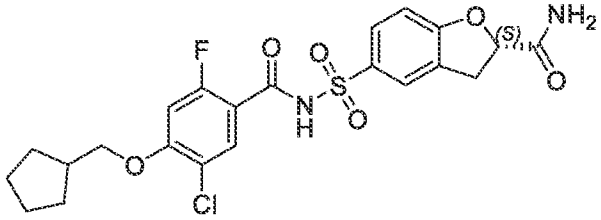
Example 276: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-cyclopropoxyphenyl)sulfonyl)-2-fluorobenzamide



(I)

[0610] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzene-sulfonamide with 4-cyclopropoxybenzenesulfonamide. The title compound was obtained. LCMS (ESI) m/z: 468.1 $[M+H]^+$.

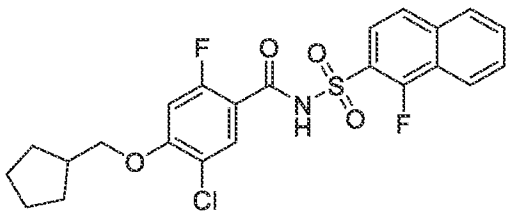
Example 277: (*S*)-5-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)-2,3-dihydrobenzofuran-2-carboxamide



(I)

[0611] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with (*S*)-5-sulfamoyl-2,3-dihydrobenzofuran-2-carboxamide. The title compound was obtained. LCMS (ESI) m/z: 497.2 $[M+H]^+$.

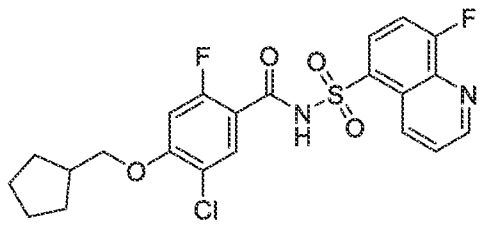
Example 278: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((1-fluoronaphthalen-2-yl)sulfonyl)benzamide



(I)

[0612] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with 1-fluoronaphthalene-2-sulfonamide. The title compound was obtained. LCMS (ESI) m/z: 480.1 $[M+H]^+$.

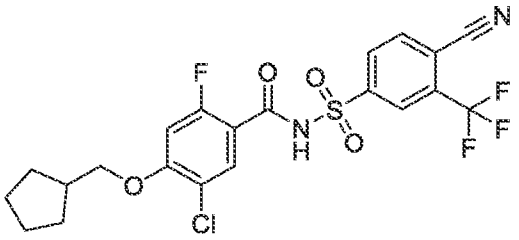
Example 279: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((8-fluoroquinolin-5-yl)sulfonyl)benzamide



(I)

[0613] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzene-sulfonamide with 8-fluoroquinoline-5-sulfonamide. The title compound was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (s, 1H), 9.16 - 9.05 (m, 2H), 8.50 - 8.38 (m, 1H), 7.92 - 7.79 (m, 2H), 7.64 (d, J = 7.6 Hz, 1H), 7.19 (d, J = 12.4 Hz, 1H), 3.99 (d, J = 6.8 Hz, 2H), 2.35 - 2.25 (m, 1H), 1.81 - 1.67 (m, 2H), 1.65 - 1.48 (m, 4H), 1.27 - 1.40 (m, 2H). LCMS (ESI) m/z: 481.1 $[M+H]^+$.

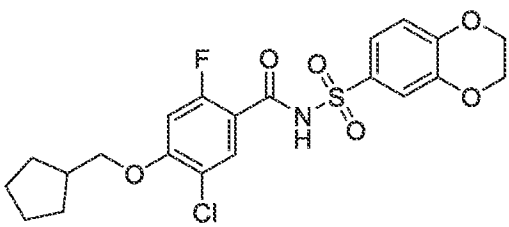
Example 280: 5-chloro-N-((4-cyano-3-(trifluoromethyl)phenyl)sulfonyl)-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

[0614] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with 4-cyano-3-(trifluoromethyl)benzenesulfonamide. The title compound was obtained. LCMS (ESI) m/z: 505.0 $[M+H]^+$.

Example 281: 5-chloro-4-(cyclopentylmethoxy)-*N*-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)sulfonyl)-2-fluorobenzamide

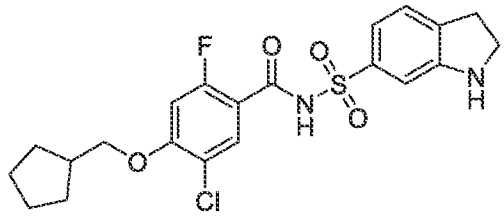


(I)

[0615] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1S,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-

difluorobenzenesulfonamide with 2,3-dihydro-1,4-benzodioxine-6-sulfonamide. The title compound was obtained. LCMS (ESI) m/z: 470.1 $[M+H]^+$.

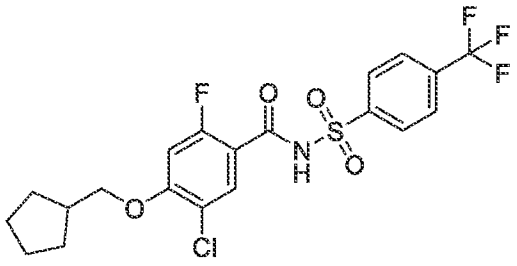
Example 282: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(indolin-6-ylsulfonyl)benzamide



(I)

[0616] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with indoline-6-sulfonamide. The title compound was obtained. LCMS (ESI) m/z: 453.1 $[M+H]^+$.

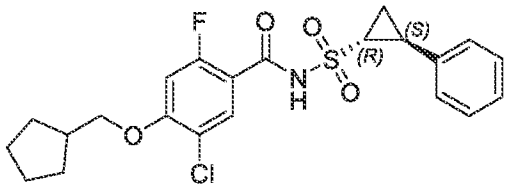
Example 283: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(trifluoromethyl)phenyl)sulfonyl)benzamide



(I)

[0617] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with 4-(trifluoromethyl)benzenesulfonamide. The title compound was obtained. LCMS (ESI) m/z: 480.1 $[M+H]^+$.

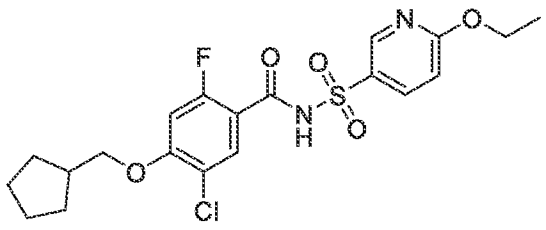
Example 284: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((*trans*-2-phenylcyclopropyl)sulfonyl)benzamide



(I)

[0618] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with *trans*-2-phenylcyclopropane-1-sulfonamide. The title compound was obtained. LCMS (ESI) m/z: 452.1 $[M+H]^+$.

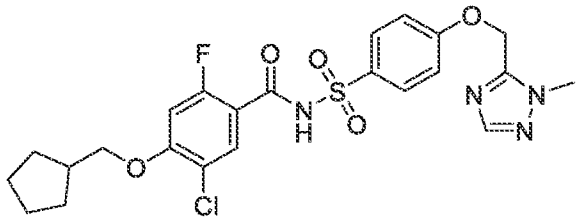
Example 285: 5-chloro-4-(cyclopentylmethoxy)-*N*-((6-ethoxypyridin-3-yl)sulfonyl)-2-fluorobenzamide



(I)

[0619] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with 6-ethoxypyridine-3-sulfonamide. The title compound was obtained. LCMS (ESI) m/z: 457.1 $[M+H]^+$.

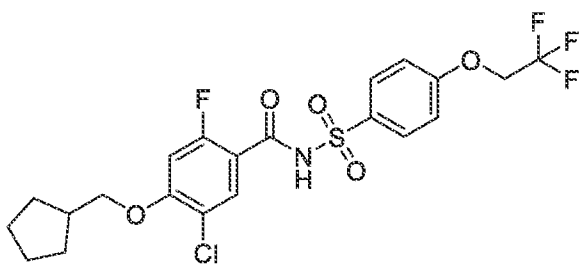
Example 286: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((1-methyl-1*H*-1,2,4-triazol-5-yl)methoxy)phenyl)sulfonyl)benzamide



(I)

[0620] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzene-sulfonamide with 4-[(1-methyl-1*H*-1,2,4-triazol-5-yl)methoxy]benzene-1-sulfonamide. The title compound was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (s, 1H), 7.99 - 7.89 (m, 3H), 7.67 (d, J = 7.2 Hz, 1H), 7.30 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 12.4 Hz, 1H), 5.44 (s, 2H), 4.01 (d, J = 7.2 Hz, 2H), 3.91 (s, 3H), 2.46 - 2.28 (m, 1H), 1.82 - 1.70 (m, 2H), 1.68 - 1.46 (m, 4H), 1.38 - 1.28 (m, 2H). LCMS (ESI) m/z: 523.1 $[M+H]^+$.

Example 287: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(2,2,2-trifluoro-ethoxy)phenyl)sulfonyl)benzamide

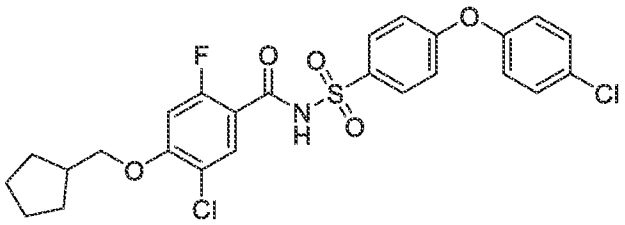


(I)

[0621] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-

difluorobenzenesulfonamide with 4-(2,2,2-trifluoroethoxy)benzene-1-sulfonamide. The title compound was obtained. LCMS (ESI) m/z: 510.0 $[M+H]^+$.

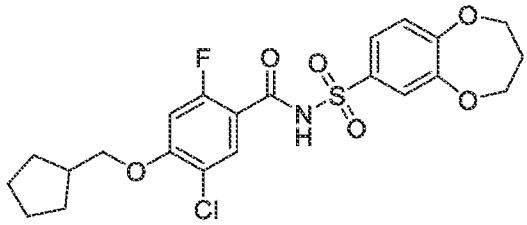
Example 288: 5-chloro-*N*-((4-(4-chlorophenoxy)phenyl)sulfonyl)-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

[0622] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with 4-(4-chlorophenoxy)benzenesulfonamide. The title compound was obtained. LCMS (ESI) m/z: 538.0 $[M+H]^+$.

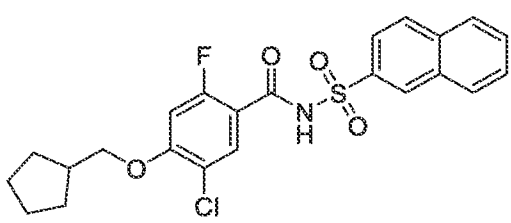
Example 289: 5-chloro-4-(cyclopentylmethoxy)-*N*-((3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)sulfonyl)-2-fluorobenzamide



(I)

[0623] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with 3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-sulfonamide. The title compound was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.39 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.53 - 7.46 (m, 2H), 7.23 (d, J = 12.8 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 4.32 - 4.18 (m, 4H), 4.02 (d, J = 6.8 Hz, 2H), 2.35 - 2.28 (m, 1H), 2.21 - 2.10 (m, 2H), 1.82 - 1.68 (m, 2H), 1.68 - 1.48 (m, 4H), 1.40 - 1.28 (m, 2H). LCMS (ESI) m/z: 484.1 $[M+H]^+$.

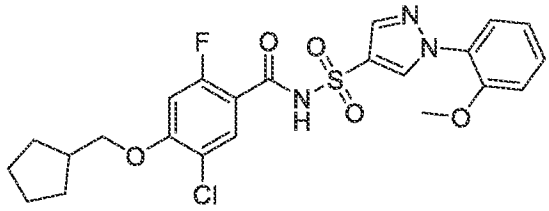
Example 290: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-(naphthalen-2-ylsulfonyl)benzamide



(I)

[0624] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with naphthalene-2-sulfonamide. The title compound was obtained. LCMS (ESI) m/z: 462.1 $[M+H]^+$.

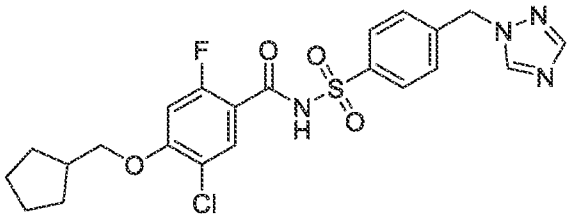
Example 291: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((1-(2-methoxyphenyl)-1*H*-pyrazol-4-yl)sulfonyl)benzamide



(I)

[0625] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with 1-(2-methoxyphenyl)-1*H*-pyrazole-4-sulfonamide. The title compound was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.50 (s, 1H), 8.78 (d, J = 3.2 Hz, 1H), 8.18 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.68 - 7.60 (m, 1H), 7.49 - 7.40 (m, 1H), 7.33 - 7.26 (m, 1H), 7.23 (d, J = 12.8 Hz, 1H), 7.13 - 7.06 (m, 1H), 4.02 (d, J = 6.8 Hz, 2H), 3.89 (s, 3H), 2.39 - 2.23 (m, 1H), 1.82 - 1.69 (m, 2H), 1.67 - 1.46 (m, 4H), 1.40 - 1.26 (m, 2H). LCMS (ESI) m/z: 508.1 $[M+H]^+$.

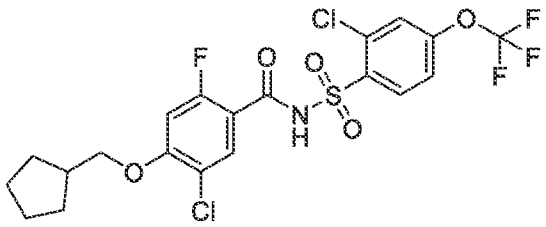
Example 292: N-((4-((1H-1,2,4-triazol-1-yl)methyl)phenyl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

[0626] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with 4-[(1*H*-1,2,4-triazol-1-yl)methyl]benzene-1-sulfonamide. The title compound was obtained. LCMS (ESI) m/z: 493.1 $[M+H]^+$.

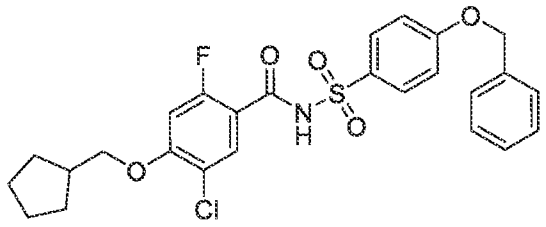
Example 293: 5-chloro-*N*-((2-chloro-4-(trifluoromethoxy)phenyl)sulfonyl)-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

[0627] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with 2-chloro-4-(trifluoromethoxy)benzene-1-sulfonamide. The title compound was obtained. LCMS (ESI) m/z: 530.0 $[M+H]^+$.

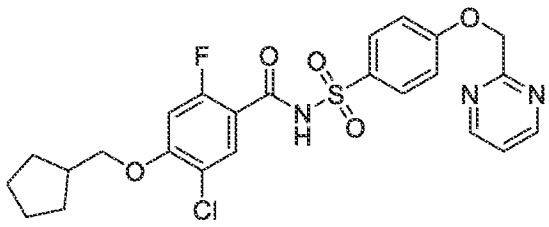
Example 294: *N*-((4-(benzyloxy)phenyl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

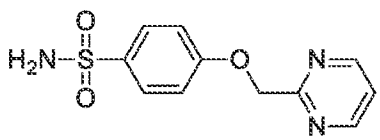
[0628] Following the procedure described in **Example 204** and making non-critical variations as required to replace 4-(((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorobenzenesulfonamide with 4-(benzyloxy)benzenesulfonamide. The title compound was obtained. LCMS (ESI) m/z: 518.1.1 $[M+H]^+$.

Example 295: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-(pyrimidin-2-ylmethoxy)phenyl)sulfonyl)benzamide



(I)

Step 1: 4-[(pyrimidin-2-yl)methoxy]benzene-1-sulfonamide

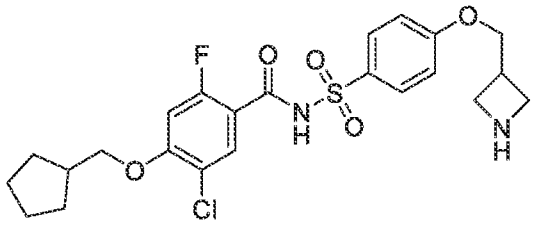


[0629] To a solution of 4-hydroxybenzenesulfonamide (39 mg, 0.23 mmol) and 2-(chloromethyl)pyrimidine (58 mg, 0.45 mmol) in DMF (1 mL) was added K_2CO_3 (95 mg, 0.69 mmol). The mixture was stirred at 25 °C for 16 h. The reaction was filtered and concentrated in vacuo to afford the title compound (30 mg, crude) that required no further purification. LCMS (ESI) m/z: 266.1 $[M+H]^+$.

Step 2: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(pyrimidin-2-ylmethoxy)phenyl)sulfonyl)benzamide

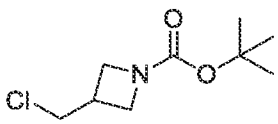
[0630] To a solution of 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid (27 mg, 0.10 mmol) in DCM (1 mL) was added EDCI (23 mg, 0.12 mmol). The mixture was stirred at 30 °C for 2 h before the addition of 4-[(pyrimidin-2-yl)methoxy]benzene-1-sulfonamide (30 mg, 0.12 mmol) and DMAP (18 mg, 0.15 mmol). The reaction was then stirred at 50 °C for 16 h. After cooling to room temperature, the reaction was concentrated in vacuo and the crude residue was purified by reverse phase chromatography (acetonitrile 30 - 70% / 0.2% formic acid in water) to afford the title compound (5 mg, 9%). LCMS (ESI) m/z: 520.1 $[M+H]^+$.

Example 296: *N*-((4-(azetidin-3-ylmethoxy)phenyl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide



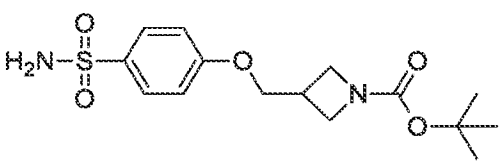
(I)

Step 1: *tert*-butyl 3-(chloromethyl)azetidine-1-carboxylate



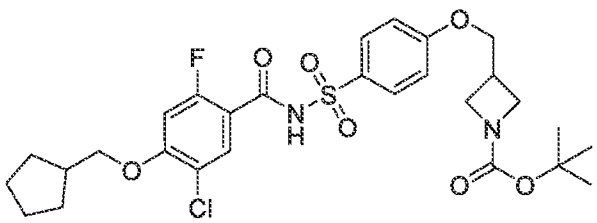
[0631] To a solution of *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (93.5 mg, 0.50 mmol) in DCM (2.5 mL) was added $SOCl_2$ (0.5 mL) at 0 °C. The mixture was stirred at 50 °C for 2 h. The reaction was concentrated in vacuo to afford the title compound (82.0 mg, crude) that required no further purification. LCMS (ESI) m/z: 206.09 $[M+H]^+$.

Step 2: *tert*-butyl 3-((4-sulfamoylphenoxy)methyl)azetidine-1-carboxylate



[0632] To a solution of 4-hydroxybenzenesulfonamide (52 mg, 0.30 mmol) and *tert*-butyl 3-(chloromethyl)azetidine-1-carboxylate (82 mg, 0.40 mmol) in DMF (2 mL) was added Cs_2CO_3 (293 mg, 0.90 mmol). The mixture was stirred at 50 °C for 16 h. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated in vacuo to afford the title compound (86 mg, crude) that required no further purification. LCMS (ESI) m/z: 343.1 $[M+H]^+$.

Step 3: *tert*-butyl 3-((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)phenoxy)methyl)azetidine-1-carboxylate

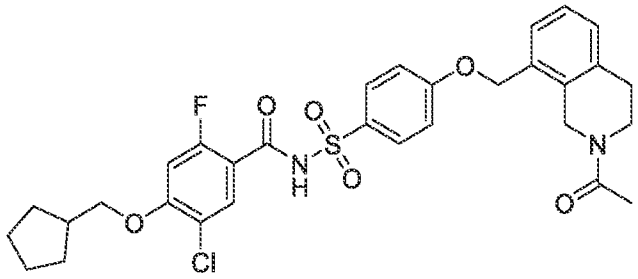


[0633] To a solution of 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid (54 mg, 0.20 mmol) in DCM (1 mL) was added EDCI (46 mg, 0.24 mmol). The mixture was stirred at 30 °C for 2 h before the addition of *tert*-butyl 3-((4-sulfamoylphenoxy)methyl)azetidine-1-carboxylate (86 mg, 0.25 mmol) and DMAP (37 mg, 0.30 mmol). The reaction was then stirred at 50 °C for 16 h. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated in vacuo to afford the title compound (89 mg, crude) that required no further purification. LCMS (ESI) m/z: 597.2 $[M+H]^+$.

Step 4: *N*-((4-(azetidin-3-ylmethoxy)phenyl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide

[0634] To a solution of *tert*-butyl 3-((4-(*N*-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)phenoxy)methyl)azetidine-1-carboxylate (89 mg, 0.15 mmol) in DCM (0.9 mL) was added TFA (0.3 mL). The mixture was stirred at 30 °C for 3 h. The mixture was concentrated in vacuo and the crude residue was purified by reverse phase chromatography (acetonitrile 15 - 45% / 0.2% formic acid in water) to afford the title compound (3.0 mg, 6%). LCMS (ESI) m/z: 497.1 $[M+H]^+$.

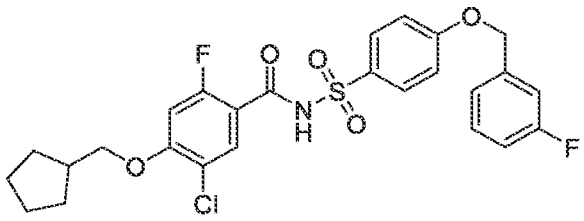
Example 297: *N*-((4-((2-acetyl-1,2,3,4-tetrahydroisoquinolin-8-yl)methoxy)phenyl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

[0635] Following the procedure described in **Example 296** and making non-critical variations as required to replace *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate with 1-(8-(hydroxymethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)ethanone. The title compound was obtained. LCMS (ESI) m/z: 615.1 $[M+H]^+$.

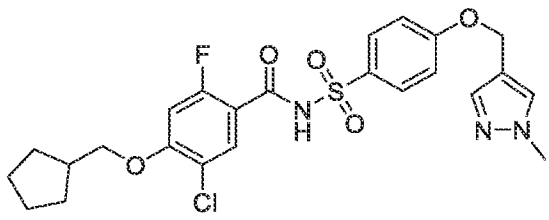
Example 298: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((3-fluorobenzyl)oxy)-phenyl)sulfonyl)benzamide



(I)

[0636] Following the procedure described in **Example 295** and making non-critical variations as required to replace 2-(chloromethyl)pyrimidine with 1-(chloromethyl)-3-fluorobenzene. The title compound was obtained. LCMS (ESI) m/z: 536.1 $[M+H]^+$.

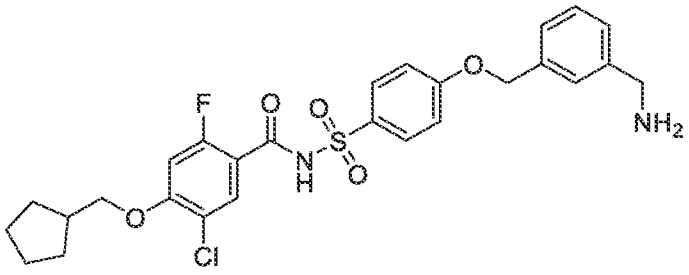
Example 299: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((1-methyl-1*H*-pyrazol-4-yl)methoxy)phenyl)sulfonyl)benzamide



(I)

[0637] Following the procedure described in **Example 296** and making non-critical variations as required to replace *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate with (1-methyl-1*H*-pyrazol-4-yl)methanol. The title compound was obtained. LCMS (ESI) m/z: 522.1 $[M+H]^+$.

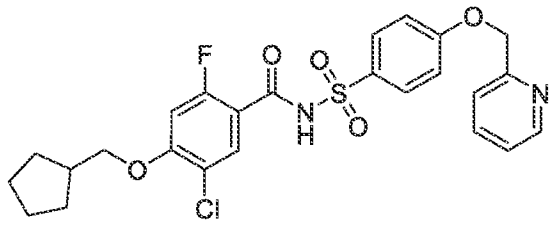
Example 300: *N*-((4-((3-(aminomethyl)benzyl)oxy)phenyl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

[0638] Following the procedure described in **Example 296** and making non-critical variations as required to replace *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate with *tert*-butyl 3-(hydroxymethyl)benzylcarbamate. The title compound was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 2H), 7.77 - 7.70 (m, 3H), 7.60 - 7.36 (m, 4H), 7.00 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 12.4 Hz, 1H), 5.17 (s, 2H), 4.06 (s, 2H), 3.94 (d, J = 6.8 Hz, 2H), 2.36 - 2.28 (m, 1H), 1.80 - 1.68 (m, 2H), 1.67 - 1.47 (m, 4H), 1.40 - 1.30 (m, 2H). LCMS (ESI) m/z: 547.1 $[M+H]^+$.

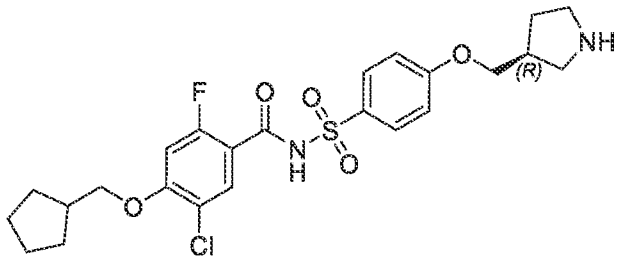
Example 301: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(pyridin-2-ylmethoxy)phenyl)sulfonyl)benzamide



(I)

[0639] Following the procedure described in **Example 96** and making non-critical variations as required to replace *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate with pyridin-2-ylmethanol. The title compound was obtained. LCMS (ESI) m/z: 519.1 $[M+H]^+$.

Example 302: (*R*)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(pyrrolidin-3-ylmethoxy)phenyl)sulfonyl)benzamide

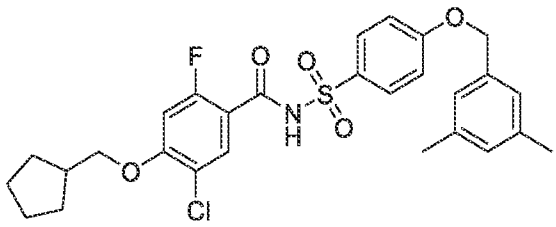


(I)

[0640] Following the procedure described in **Example 296** and making non-critical variations as required to replace *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate with *tert*-butyl (*R*)-3-

(hydroxymethyl)pyrrolidine-1-carboxylate. The title compound was obtained. LCMS (ESI) m/z: 511.1 $[M+H]^+$.

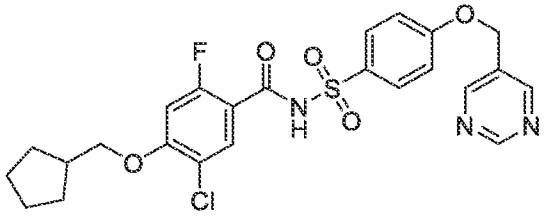
Example 303: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-((3,5-dimethylbenzyl)oxy)phenyl)sulfonyl)-2-fluorobenzamide



(I)

[0641] Following the procedure described in **Example 295** and making non-critical variations as required to replace 2-(chloromethyl)pyrimidine with 1-(chloromethyl)-3,5-dimethylbenzene. The title compound was obtained. LCMS (ESI) m/z: 546.1 $[M+H]^+$.

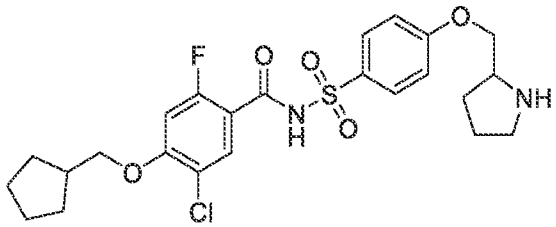
Example 304: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(pyrimidin-5-ylmethoxy)phenyl)sulfonyl)benzamide



(I)

[0642] Following the procedure described in **Example 295** and making non-critical variations as required to replace *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate with pyrimidin-5-ylmethanol. The title compound was obtained. LCMS (ESI) m/z: 520.0 $[M+H]^+$.

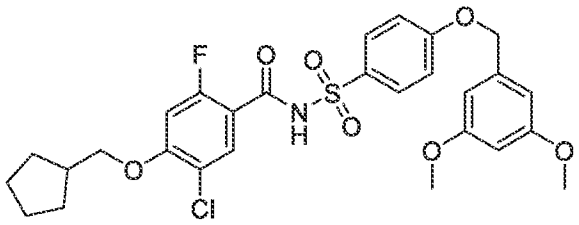
Example 305: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(pyrrolidin-2-ylmethoxy)phenyl)sulfonyl)benzamide



(I)

[0643] Following the procedure described in **Example 296** and making non-critical variations as required to replace *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate with *tert*-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate. The title compound was obtained. LCMS (ESI) m/z: 511.1 $[M+H]^+$.

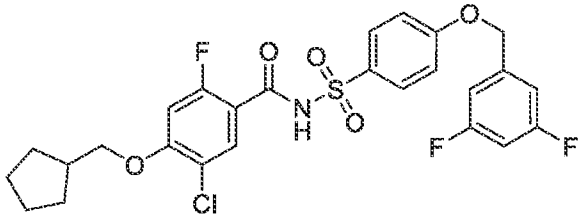
Example 306: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-((3,5-dimethoxybenzyl)oxy)phenyl)sulfonyl)-2-fluorobenzamide



(I)

[0644] Following the procedure described in **Example 295** and making non-critical variations as required to replace 2-(chloromethyl)pyrimidine with 1-(chloromethyl)-3,5-dimethoxybenzene. The title compound was obtained. LCMS (ESI) m/z: 578.1 $[M+H]^+$.

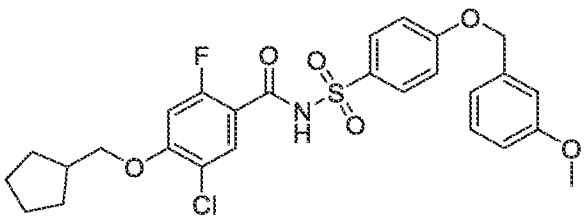
Example 307: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-((3,5-difluorobenzyl)oxy)phenyl)sulfonyl)-2-fluorobenzamide



(I)

[0645] Following the procedure described in **Example 295** and making non-critical variations as required to replace 2-(chloromethyl)pyrimidine with 1-(chloromethyl)-3,5-difluorobenzene. The title compound was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (s, 1H), 7.91 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 7.6 Hz, 1H), 7.26 - 7.15 (m, 6H), 5.24 (s, 2H), 4.00 (d, J = 6.8 Hz, 2H), 2.38 - 2.22 (m, 1H), 1.81 - 1.70 (m, 2H), 1.68 - 1.42 (m, 4H), 1.39 - 1.28 (m, 2H). LCMS (ESI) m/z: 554.1 $[M+H]^+$.

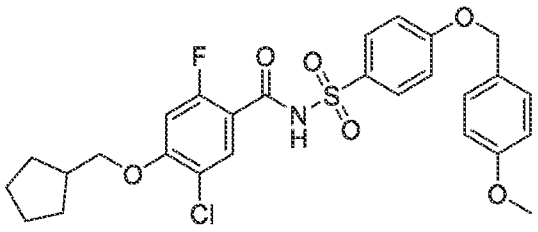
Example 308: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((3-methoxybenzyl)oxy)phenyl)sulfonyl)benzamide



(I)

[0646] Following the procedure described in **Example 295** and making non-critical variations as required to replace 2-(chloromethyl)pyrimidine with 1-(chloromethyl)-3-methoxybenzene. The title compound was obtained. LCMS (ESI) m/z: 548.1 $[M+H]^+$.

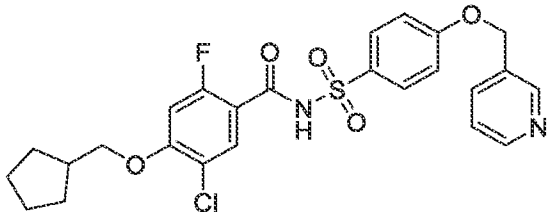
Example 309: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((4-methoxybenzyl)oxy)phenyl)sulfonyl)benzamide



(I)

[0647] Following the procedure described in **Example 295** and making non-critical variations as required to replace 2-(chloromethyl)pyrimidine with 1-(chloromethyl)-4-methoxybenzene. The title compound was obtained. LCMS (ESI) m/z: 548.1 $[M+H]^+$.

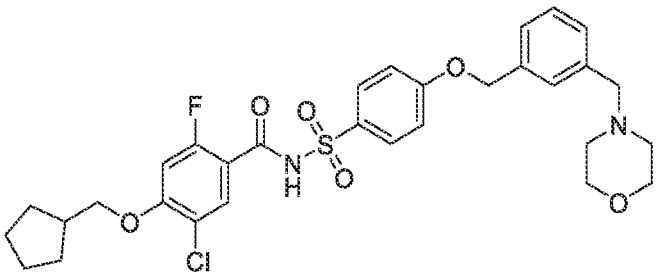
Example 310: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(pyridin-3-ylmethoxy)phenyl)sulfonyl)benzamide



(I)

[0648] Following the procedure described in **Example 296** and making non-critical variations as required to replace *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate with pyridin-3-ylmethanol. The title compound was obtained. LCMS (ESI) m/z: 519.1 $[M+H]^+$.

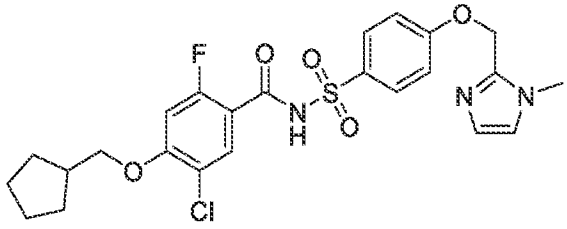
Example 311: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((3-(morpholinomethyl)benzyl)oxy)phenyl)sulfonyl)benzamide



(I)

[0649] Following the procedure described in **Example 296** and making non-critical variations as required to replace *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate with (3-(morpholinomethyl)phenyl)methanol. The title compound was obtained. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.36 (s, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.0 Hz, 1H), 7.49 - 7.33 (m, 4H), 7.22 - 7.05 (m, 3H), 5.21 (s, 2H), 3.98 (d, J = 6.8 Hz, 2H), 3.85 (s, 2H), 3.68 - 3.59 (m, 4H), 2.80 - 2.56 (m, 4H), 2.38 - 2.26 (m, 1H), 1.81 - 1.72 (m, 2H), 1.65 - 1.48 (m, 4H), 1.39 - 1.29 (m, 2H). LCMS (ESI) m/z: 617.1 $[M+H]^+$.

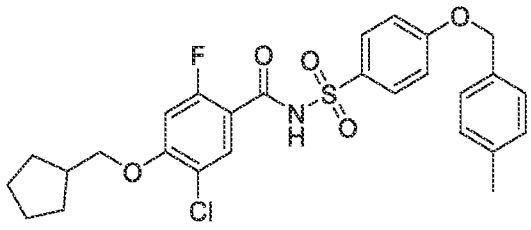
Example 312: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((1-methyl-1H-imidazol-2-yl)methoxy)phenyl)sulfonyl)benzamide



(I)

[0650] Following the procedure described in **Example 295** and making non-critical variations as required to replace 2-(chloromethyl)pyrimidine with 2-(chloromethyl)-1-methyl-1*H*-imidazole. The title compound was obtained. LCMS (ESI) m/z: 522.1 $[M+H]^+$.

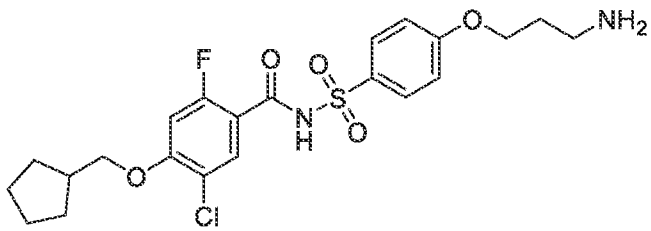
Example 313: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((4-methylbenzyl)oxy)phenyl)sulfonyl)benzamide



(I)

[0651] Following the procedure described in **Example 295** and making non-critical variations as required to replace 2-(chloromethyl)pyrimidine with 1-(chloromethyl)-4-methylbenzene. The title compound was obtained. LCMS (ESI) m/z: 532.1 $[M+H]^+$.

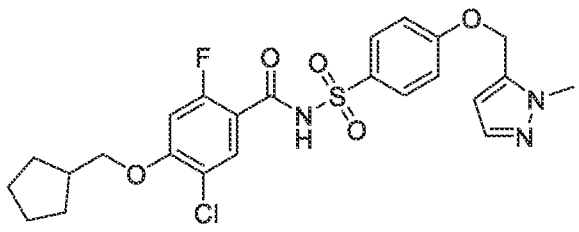
Example 314: *N*-((4-(3-aminopropoxy)phenyl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide



(I)

[0652] Following the procedure described in **Example 296** and making non-critical variations as required to replace *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate with *tert*-butyl (3-hydroxypropyl)carbamate. The title compound was obtained. LCMS (ESI) m/z: 485.1 $[M+H]^+$.

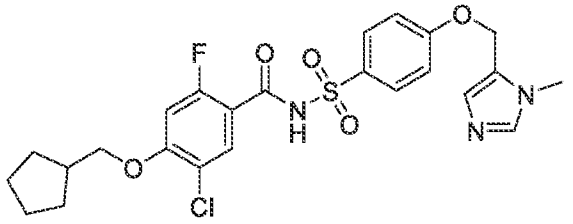
Example 315: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((1-methyl-1*H*-pyrazol-5-yl)methoxy)phenyl)sulfonyl)benzamide



(I)

[0653] Following the procedure described in **Example 296** and making non-critical variations as required to replace *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate with (1-methyl-1H-pyrazol-5-yl)methanol. The title compound was obtained. LCMS (ESI) m/z: 522.1 $[M+H]^+$.

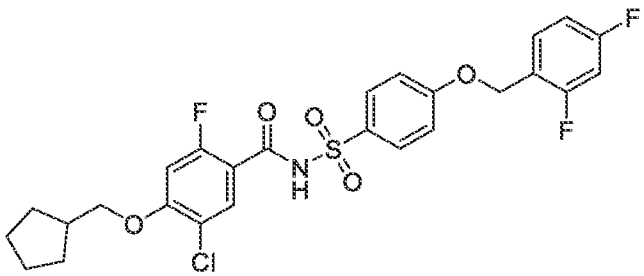
Example 316: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((1-methyl-1*H*-imidazol-5-yl)methoxy)phenyl)sulfonyl)benzamide



(I)

[0654] Following the procedure described in **Example 296** and making non-critical variations as required to replace *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate with (1-methyl-1H-imidazol-5-yl)methanol. The title compound was obtained. LCMS (ESI) m/z: 522.1 $[M+H]^+$.

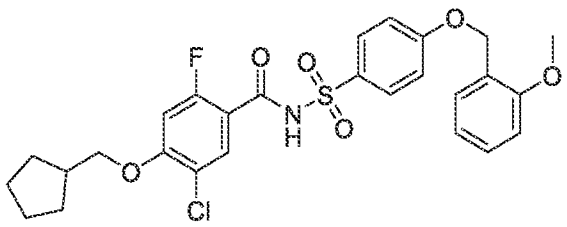
Example 317: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-((2,4-difluorobenzyl)oxy)phenyl)sulfonyl)-2-fluorobenzamide



(I)

[0655] Following the procedure described in **Example 295** and making non-critical variations as required to replace 2-(chloromethyl)pyrimidine with 1-(chloromethyl)-2,4-difluorobenzene. The title compound was obtained. LCMS (ESI) m/z: 554.1 $[M+H]^+$.

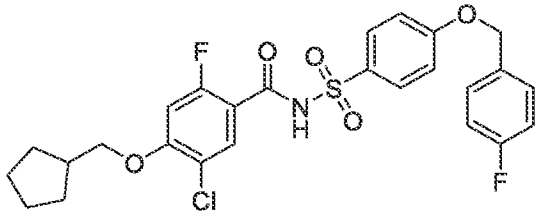
Example 318: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((2-methoxybenzyl)oxy)phenyl)sulfonyl)benzamide



(I)

[0656] Following the procedure described in **Example 295** and making non-critical variations as required to replace 2-(chloromethyl)pyrimidine with 1-(chloromethyl)-2-methoxybenzene. The title compound was obtained. LCMS (ESI) m/z: 548.1 $[M+H]^+$.

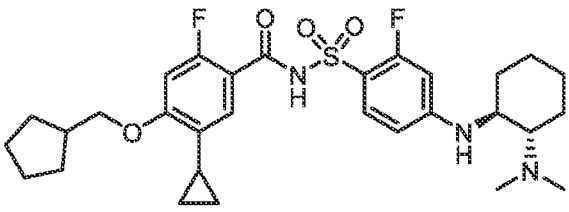
Example 319: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-((4-fluorobenzyl)oxy)phenyl)sulfonyl)benzamide



(I)

[0657] Following the procedure described in **Example 295** and making non-critical variations as required to replace 2-(chloromethyl)pyrimidine with 1-(chloromethyl)-4-fluorobenzene. The title compound was obtained. LCMS (ESI) m/z: 536.1 $[M+H]^+$.

Example 320: 4-(cyclopentylmethoxy)-5-cyclopropyl-N-((4-(((1S,2S)-2-(dimethylamino)cyclohexyl)amino)-2-fluorophenyl)sulfonyl)-2-fluorobenzamide



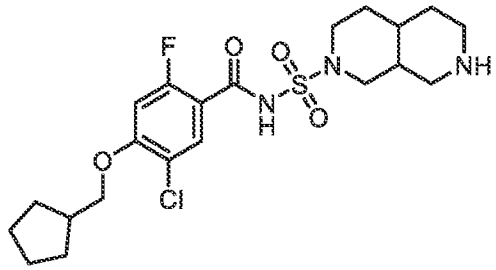
(I)

[0658] Following the procedure described in compound **206** and replacing 5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoic acid with 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzoic acid, the title compound was obtained as a white solid.

[0659] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (t, J = 8.8 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 6.65 (d, J = 12.0 Hz, 1H), 6.52 - 6.34 (m, 2H), 5.99 (s, 1H), 3.87 (d, J = 6.8 Hz, 2H), 3.72 - 3.52 (m, 1H), 3.05 - 2.81 (m, 1H), 2.61 - 2.52 (m, 6H), 2.37 - 2.26 (m, 1H), 2.07 - 1.90 (m, 3H), 1.87 - 1.71 (m, 3H), 1.66 - 1.52 (m, 5H), 1.45 - 1.30 (m, 4H), 1.29 - 1.20 (m, 1H), 1.15 - 1.05 (m, 1H),

0.91 - 0.80 (m, 2H), 0.60 - 0.45 (m, 2H). HRMS *m/z* calcd for $C_{30}H_{39}F_2N_3O_4S$ $[M+H]^+$: 576.2702. Fogund 576.2713.

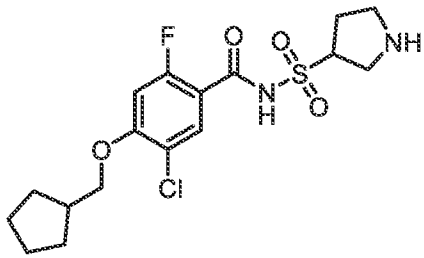
Example 321: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((octahydro-2,7-naphthyridin-2(1H)-yl)sulfonyl)benzamide



(I)

[0660] The compound of Example 321 was prepared according to the methods developed and depoloyed for other compounds herein.

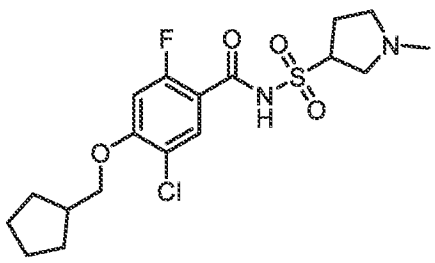
Example 322: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(pyrrolidin-3-ylsulfonyl)-benzamide



(I)

[0661] The compound of Example 322 was prepared according to the methods developed and depoloyed for other compounds herein.

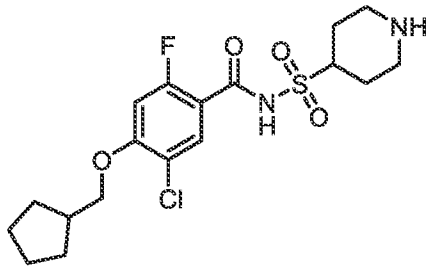
Example 323: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((1-methylpyrrolidin-3-yl)sulfonyl)benzamide



(I)

[0662] The compound of Example 323 was prepared according to the methods developed and depoloyed for other compounds herein.

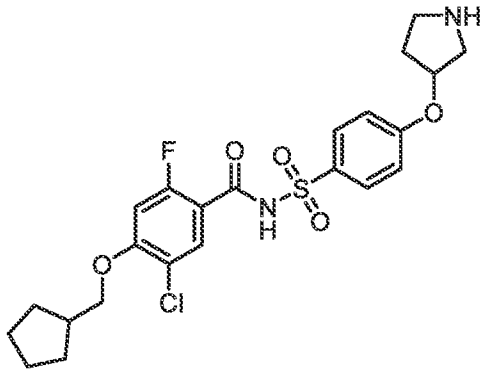
Example 324: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(piperidin-4-ylsulfonyl)-benzamide



(I)

[0663] The compound of Example 324 was prepared according to the methods developed and depoloyed for other compounds herein.

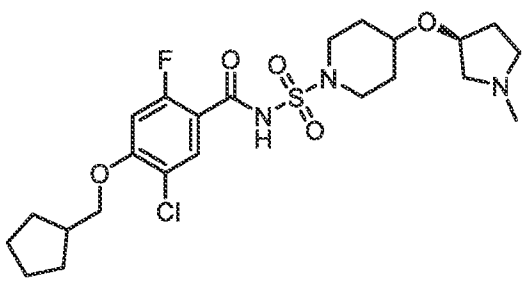
Example 325: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-(pyrrolidin-3-yloxy)phenyl)sulfonyl)benzamide



(I)

[0664] The compound of Example 325 was prepared according to the methods developed and depoloyed for other compounds herein.

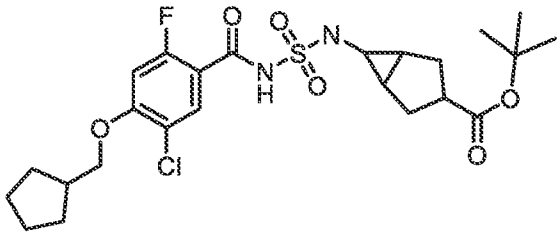
Example 326: (S)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((1-methylpyrrolidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide



(I)

[0665] The compound of Example 326 was prepared according to the methods developed and depoloyed for other compounds herein.

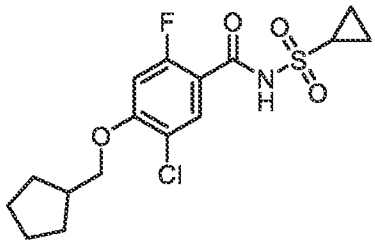
Example 327: tert-butyl 6-((N-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)-sulfamoyl)amino)bicyclo[3.1.0]hexane-3-carboxylate



(I)

[0666] The compound of Example 327 was prepared according to the methods developed and depoloyed for other compounds herein.

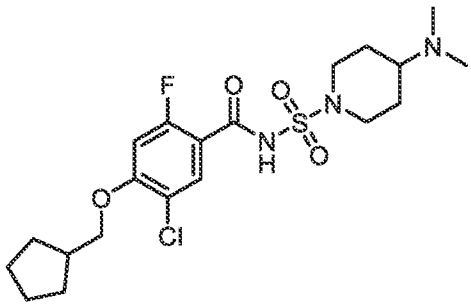
Example 328: 5-chloro-4-(cyclopentylmethoxy)-N-(cyclopropylsulfonyl)-2-fluorobenzamide



(I)

[0667] The compound of Example 328 was prepared according to the methods developed and depoloyed for other compounds herein.

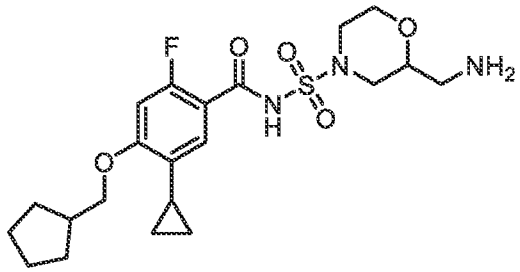
Example 329: 5-chloro-4-(cyclopentylmethoxy)-N-((4-(dimethylamino)piperidin-1-yl)sulfonyl)-2-fluorobenzamide



(I)

[0668] The compound of Example 329 was prepared according to the methods developed and depoloyed for other compounds herein.

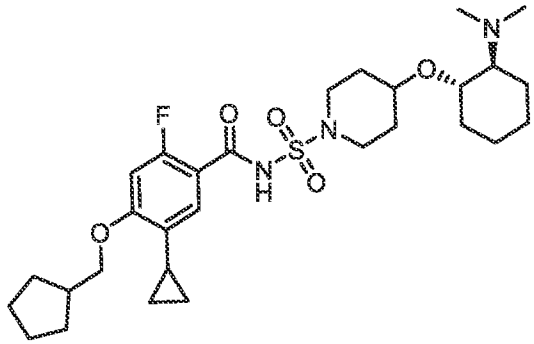
Example 330: N-((2-(aminomethyl)morpholino)sulfonyl)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzamide



(I)

[0669] The compound of Example 330 was prepared according to the methods developed and depoloyed for other compounds herein.

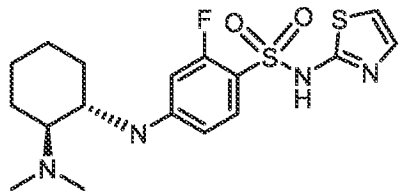
Example 331: 4-(cyclopentylmethoxy)-5-cyclopropyl-N-((4-(((1S,2S)-2-(dimethylamino)cyclohexyl)oxy)piperidin-1-yl)sulfonyl)-2-fluorobenzamide



(I)

[0670] The compound of Example 331 was prepared according to the methods developed and depoloyed for other compounds herein.

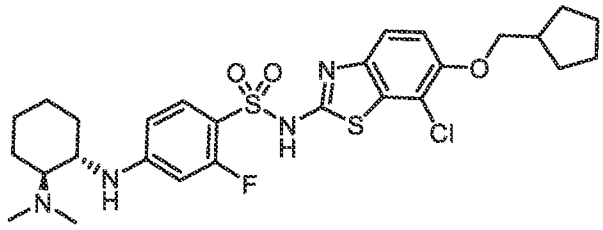
Example 332: 4-(((1S,2S)-2-(dimethylamino)cyclohexyl)amino)-2-fluoro-N-(thiazol-2-yl)benzenesulfonamide



(II)

[0671] The compound of Example 332 was prepared according to the methods developed and depoloyed for other compounds herein.

Example 333: N-(7-chloro-6-(cyclopentylmethoxy)benzo[d]thiazol-2-yl)-4-(((1S,2S)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzenesulfonamide



(II)

[0672] The compound of Example 333 was prepared according to the methods developed and depoloyed for other compounds herein.

Example 400: Electrophysiological Assay (EP) (*in vitro* assay)

[0673] Patch voltage clamp electrophysiology allows for the direct measurement and quantification of block of voltage-gated sodium channels (NaV's), and allows the determination of the time- and voltage-dependence of block which has been interpreted as differential binding to the resting, open, and inactivated states of the sodium channel (Hille, B., *Journal of General Physiology* (1977), 69: 497-515).

[0674] The following voltage clamp electrophysiology studies are performed on representative compounds using cells heterologously expressing Nav1.7 or Nav1.5 channels. cDNAsfor Nav1.7 (NM_002977) and Nav1.5 (AC137587) are stably expressed in Chinese Hamstr Ovary (CHO) cells and CHL (Chinese Hamster Lung) cells respectively. Sodium currents are measured in the whole-cell configuration using Syncropatch 384PE (NanIon Technologies, Germany). 1NPC®-384 chips with custom medium resistance and single hole mode are used. Internal solution consists of (in mM): 110 CsCl, 10 CsCl, 20 EGTA, and 10 Hepes (pH adjusted to 7.2); and external solution contains (in mM): 60 NMDG, 80 NaCl, 4 KCl, 1 $MgCl_2$, 2 $CaCl_2$, 2 D-Glucose monohydrate, 10 Hepes (pH adjusted to 7.4 with NaOH).

[0675] After system flushing, testing compounds are dissolved in external solution containing 0.1% Pluronic F-127. The chip is moved into the measuring head and the instrument primes the chip with external and internal solutions. 10 µl cells are added to the chip from a cell hotel, and a negative pressure of −50 mBar is applied to form a seal. Following treatment with seal enhancer solution and wash-off with external solution, negative pressure of −250 mbar is applied for 1 second to achieve the whole-cell configuration, followed by three washing steps in external solution. 20µl of compounds is added to 40µl in each well (1:3 dilution of compounds), and after mixing, 20µl is removed so the volume is retained at 40 ul. After approximately 13 minutes

recordings, 20µl/well of 2 µM TTX, or 333 µM Tetracaine (for Nav1.5) is added to achieve full block.

[0676] For voltage protocol, an holding potential of -50 mV is applied during the whole experiment. A depolarizing step is applied to-10mV for 10ms, followed by a hyperpolarization step to -150 mV for 20 ms to allow channel recovery from inactivation. A second depolarizing step is applied from -150 mV to -10 mV for 10 ms, where currents are measured to derive blocking effects of compounds. Inhibition is determined based on 7.5 min. of compound incubation.

[0677] Data for representative compounds is provided in Table 1. Compounds in the following table that are not prepared in the Examples above were prepared using synthetic schemes and reagents similar to those used in the Examples.

Table 1

Formula	Example	Comment	hNaV1.7 EP_SP (µM)
I	1		0.11
I	2		0.064
I	3		0.022
I	4		0.015
I	5		0.039
I	6		0.32
I	7		0.008
I	9		0.059
I	10		0.031
I	11		0.13
I	12		0.029
I	13		0.24
I	14		0.078
I	15		0.11
I	16		0.24
I	17		0.1
I		*(S) enantiomer of Example 18*	0.5
I	18		0.024
I	19		0.31
I	20		0.049

Formula	Example	Comment	hNaV1.7 EP_SP (μM)
I	21		0.014
I	22		0.0091
I	23		0.11
I	24		0.1
I	25		0.015
I	26		0.19
I	27		0.09
I		*(S) enantiomer of Example 27*	0.4
I	28		0.23
I	29		0.027
I	30		0.016
I	31		0.39
I	36		0.2
I	37		0.077
I	38		0.039
I	40		0.059
I	41		0.17
I	44		0.13
I	46		0.25
I	47		0.036
I	48		0.86
I	49		0.86
I	50		0.26
I	51		0.068
I	52		0.17
I	53		0.25
I	57		0.54
I	58		0.32
I	59		0.047
I	62		0.017
I	63		0.016
I	64		0.29
I	65		0.025
I	66		0.22

Formula	Example	Comment	hNaV1.7 EP_SP (μM)
I	69		0.13
I	70		0.06
I	72		0.34
I	74		0.0055
I	75		0.12
I	76		0.032
I	78		0.1
I	79		0.1
I	80		0.7
I	81		0.14
I	82		0.03
I	83		0.092
I	84		0.69
I	85		0.016
I	86		0.1
I	87		0.39
III	89		0.34
III	90		0.4
III	91		0.79
III	92		0.069
III	93		0.11
III	94		0.24
II	95		0.17
II	96		0.0088
II	97		0.02
II	99		0.43
II	101		0.48
II	102		0.65
II	103		0.22
	107		0.99
II	201		0.37
II	202		0.022
II	203		0.074
I	204		0.01

Formula	Example	Comment	hNaV1.7 EP_SP (μM)
I	205		0.039
I	206		0.05
I	208		0.88
I	209		0.11
I	212		0.087
I	213		0.42
I	217		0.37
I	218		0.56
I	219		0.65
I	*220*		0.014
I	*221*		0.016
I	222		0.033
I	223		0.039
I	224		0.04
I	225		0.01
I	226		0.75
I	227		0.02
I	228		0.21
I	229		0.012
I	230		0.063
I	231		0.43
I	232		0.88
I	233		0.87
I	234		0.34
I	236		0.039
I	237		0.05
I	238		0.084
I	239		0.025
I	241		0.065
I	242		0.11
I	243		0.67
I	244		0.77
I	245		0.69
I	246		0.23

Formula	Example	Comment	hNaV1.7 EP_SP (μM)
I	247		0.052
I	248		0.76
I	249		0.11
I	250		0.0098
I	251		0.016
I	252		0.11
I	253		0.42
I	254		0.014
I	255		0.026
I	256		0.013
II	257		0.73
II	258		0.83
I	259		0.79
I	260		0.2
I	261		0.53
I	262		0.27
I	263		0.22
I	264		0.084
I	265		0.33
I	266		0.13
I	267		0.8
I	268		0.088
I	269		0.94
I	270		0.38
I	271		0.26
I	272		0.21
I	273		0.23
I	274		0.23
I	275		0.51
I	276		0.13
I	277		0.59
I	278		0.96
I	279		0.5
I	280		0.71

Formula	Example	Comment	hNaV1.7 EP_SP (μM)
I	281		0.32
I	282		0.76
I	283		0.62
I	284		0.12
I	285		0.35
I	286		0.16
I	287		0.25
I	288		0.49
I	289		0.71
I	290		0.76
I	291		0.35
I	292		0.43
I	293		0.85
I	294		0.13
I	295		0.23
I	296		0.28
I	297		0.022
I	298		0.22
I	299		0.038
I	300		0.0032
I	301		0.039
I	302		0.12
I	303		0.26
I	304		0.57
I	305		0.36
I	306		0.17
I	307		0.73
I	308		0.1
I	309		0.12
I	310		0.018
I	311		0.023
I	312		0.083
I	313		0.14
I	314		0.31

Formula	Example	Comment	hNaV1.7 EP_SP (μM)
I	315		0.047
I	316		0.028
I	317		0.25
I	318		0.19
I	319		0.11
I	320		0.012
I	321		0.21
I	322		0.51
I	323		0.47
I	324		0.79
I	325		0.24
I	326		0.23
I	327		0.92
I	328		0.01
I	329		1
I	330		0.62
I	331		0.14
II	332		0.22
II	333		0.065

Example 401: Analgesia Induced by Sodium Channel Blockers

[0678] This example describes experimental protocols that can be employed to test efficacy of the compounds disclosed herein.

Heat Induced Tail Flick Latency Test

[0679] In this test, the analgesia effect produced by administering a compound of the invention can be observed through heat-induced tail-flick in mice. The test includes a heat source consisting of a projector lamp with a light beam focused and directed to a point on the tail of a mouse being tested. The tail-flick latencies, which are assessed prior to drug treatment, and in response to a noxious heat stimulus, i.e., the response time from applying radiant heat on the dorsal surface of the tail to the occurrence of tail flick, are measured and recorded at 40, 80, 120, and 160 minutes.

[0680] For the first part of this study, 65 animals undergo assessment of baseline tail flick latency once a day over two consecutive days. These animals are then randomly assigned to one

of the 11 different treatment groups including a vehicle control, a morphine control, and 9 compounds at 30 mg/Kg are administered intramuscularly. Following dose administration, the animals are closely monitored for signs of toxicity including tremor or seizure, hyperactivity, shallow, rapid or depressed breathing and failure to groom. The optimal incubation time for each compound is determined via regression analysis. The analgesic activity of the test compounds is expressed as a percentage of the maximum possible effect (%MPE) and is calculated using the following formula:

$$\%\ \text{MPE} \quad \frac{\text{Postdrug latency - Predrug latency}}{\text{Cut-off time (10 s) - Predrug latency}} \times 100\%$$

where:

Postdrug latency = the latency time for each individual animal taken before the tail is removed (flicked) from the heat source after receiving drug.

Predrug latency = the latency time for each individual animal taken before the tail is flicked from the heat source prior to receiving drug.

Cut-off time (10 s) = is the maximum exposure to the heat source.

Acute Pain (Formalin Test)

[0681] The formalin test is used as an animal model of acute pain. In the formalin test, animals are briefly habituated to the plexiglass test chamber on the day prior to experimental day for 20 minutes. On the test day, animals are randomly injected with the test articles. At 30 minutes after drug administration, 50 µL of 10% formalin is injected subcutaneously into the plantar surface of the left hind paw of the rats. Video data acquisition begins immediately after formalin administration, for duration of 90 minutes.

[0682] The images are captured using the Actimetrix Limelight software which stores files under the *.llii extension, and then converts it into the MPEG-4 coding. The videos are then analyzed using behaviour analysis software "The Observer 5.1", (Version 5.0, Noldus Information Technology, Wageningen, The Netherlands). The video analysis is conducted by watching the animal behaviour and scoring each according to type, and defining the length of the behaviour (Dubuisson and Dennis, 1977). Scored behaviours include: (1) normal behaviour, (2) putting no weight on the paw, (3) raising the paw, (4) licking/biting or scratching the paw. Elevation, favoring, or excessive licking, biting and scratching of the injected paw indicate a pain response. Analgesic response or protection from compounds is indicated if both paws are resting on the floor with no obvious favoring, excessive licking, biting or scratching of the injected paw.

[0683] Analysis of the formalin test data is done according to two factors: (1) Percent Maximal Potential Inhibitory Effect (%MPIE) and (2) pain score. The %MPIEs is calculated by a series of steps, where the first is to sum the length of non-normal behaviours (behaviours 1,2,3) of each animal. A single value for the vehicle group is obtained by averaging all scores within the vehicle treatment group. The following calculation yields the MPIE value for each animal:

$$\text{MPIE (\%)} = 100 - [\text{ (treatment sum/average vehicle value) X 100\% }]$$

[0684] The pain score is calculated from a weighted scale as described above. The duration of the behaviour is multiplied by the weight (rating of the severity of the response), and divided by the total length of observation to determine a pain rating for each animal. The calculation is represented by the following formula:

$$\text{Pain rating} = [\ 0(To) + 1(T1) + 2(T2) + 3(T3)\ ] / (\ To + T1 + T2 + T3\ )$$

CFA Induced Chronic Inflammatory Pain

[0685] In this test, tactile allodynia is assessed with calibrated von Frey filaments. Following a full week of acclimatization to the vivarium facility, 150 µL of the "Complete Freund's Adjuvant" (CFA) emulsion (CFA suspended in an oil/saline (1:1) emulsion at a concentration of 0.5 mg/mL) is injected subcutaneously into the plantar surface of the left hind paw of rats under light isoflurane anaesthesia. Animals are allowed to recover from the anaesthesia and the baseline thermal and mechanical nociceptive thresholds of all animals are assessed one week after the administration of CFA. All animals are habituated to the experimental equipment for 20 minutes on the day prior to the start of the experiment. The test and control articles are administrated to the animals, and the nociceptive thresholds measured at defined time points after drug administration to determine the analgesic responses to each of the six available treatments. The time points used are previously determined to show the highest analgesic effect for each test compound.

[0686] Thermal nociceptive thresholds of the animals are assessed using the Hargreaves test. Animals are placed in a Plexiglas enclosure set on top of an elevated glass platform with heating units. The glass platform is thermostatically controlled at a temperature of approximately 30 °C for all test trials. Animals are allowed to accommodate for 20 minutes following placement into the enclosure until all exploration behaviour ceases. The Model 226 Plantar/Tail Stimulator Analgesia Meter (IITC, Woodland Hills, CA) is used to apply a radiant heat beam from underneath the glass platform to the plantar surface of the hind paws. During all test trials, the

idle intensity and active intensity of the heat source are set at 1 and 45 respectively, and a cut off time of 20 seconds is employed to prevent tissue damage.

[0687] The response thresholds of animals to tactile stimuli are measured using the Model 2290 Electrovonfrey anesthesiometer (IITC Life Science, Woodland Hills, CA) following the Hargreaves test. Animals are placed in an elevated Plexiglas enclosure set on a mire mesh surface. After 10 minutes of accommodation, pre-calibrated Von Frey hairs are applied perpendicularly to the plantar surface of both paws of the animals in an ascending order starting from the 0.1 g hair, with sufficient force to cause slight buckling of the hair against the paw. Testing continues until the hair with the lowest force to induce a rapid flicking of the paw is determined or when the cut off force of approximately 20 g is reached. This cut off force is used because it represent approximately 10% of the animals' body weight and it serves to prevent raising of the entire limb due to the use of stiffer hairs, which would change the nature of the stimulus.

Postoperative Models of Nociception

[0688] In this model, the hypealgesia caused by an intra-planar incision in the paw is measured by applying increased tactile stimuli to the paw until the animal withdraws its paw from the applied stimuli. While animals are anaesthetized under 3.5% isofluorane, which is delivered via a nose cone, a 1 cm longitudinal incision is made using a number 10 scalpel blade in the plantar aspect of the left hind paw through the skin and fascia, starting 0.5 cm from the proximal edge of the heel and extending towards the toes. Following the incision, the skin is apposed using 2, 3-0 sterilized silk sutures. The injured site is covered with Polysporin and Betadine. Animals are returned to their home cage for overnight recovery.

[0689] The withdrawal thresholds of animals to tactile stimuli for both operated (ipsilateral) and unoperated (contralateral) paws can be measured using the Model 2290 Electrovonfrey anesthesiometer (IITC Life Science, Woodland Hills, CA). Animals are placed in an elevated Plexiglas enclosure set on a mire mesh surface. After at least 10 minutes of acclimatization, pre-calibrated Von Frey hairs are applied perpendicularly to the plantar surface of both paws of the animals in an ascending order starting from the 10 g hair, with sufficient force to cause slight buckling of the hair against the paw. Testing continues until the hair with the lowest force to induce a rapid flicking of the paw is determined or when the cut off force of approximately 20 g is reached. This cut off force is used because it represent approximately 10% of the animals' body

weight and it serves to prevent raising of the entire limb due to the use of stiffer hairs, which would change the nature of the stimulus.

Neuropathic pain model; Chronic Constriction Injury

[0690] Briefly, an approximately 3 cm incision is made through the skin and the fascia at the mid thigh level of the animals' left hind leg using a no. 10 scalpel blade. The left sciatic nerve is exposed via blunt dissection through the biceps femoris with care to minimize haemorrhagia. Four loose ligatures are tied along the sciatic nerve using 4-0 non-degradable sterilized silk sutures at intervals of 1 to 2 mm apart. The tension of the loose ligatures is tight enough to induce slight constriction of the sciatic nerve when viewed under a dissection microscope at a magnification of 4 fold. In the sham-operated animal, the left sciatic nerve is exposed without further manipulation. Antibacterial ointment is applied directly into the wound, and the muscle is closed using sterilized sutures. Betadine is applied onto the muscle and its surroundings, followed by skin closure with surgical clips.

[0691] The response thresholds of animals to tactile stimuli are measured using the Model 2290 Electrovonfrey anesthesiometer (IITC Life Science, Woodland Hills, CA). Animals are placed in an elevated Plexiglas enclosure set on a mire mesh surface. After 10 minutes of accommodation, pre-calibrated Von Frey hairs are applied perpendicularly to the plantar surface of both paws of the animals in an ascending order starting from the 0.1 g hair, with sufficient force to cause slight buckling of the hair against the paw. Testing continues until the hair with the lowest force to induce a rapid flicking of the paw is determined or when the cut off force of approximately 20 g is reached. This cut off force is used because it represents approximately 10% of the animals' body weight and it serves to prevent raising of the entire limb due to the use of stiffer hairs, which would change the nature of the stimulus.

[0692] Thermal nociceptive thresholds of the animals are assessed using the Hargreaves test. Following the measurement of tactile thresholds, animals are placed in a Plexiglass enclosure set on top of an elevated glass platform with heating units. The glass platform is thermostatically controlled at a temperature of approximately 24 to 26 oC for all test trials. Animals are allowed to accommodate for 10 minutes following placement into the enclosure until all exploration behaviour ceases. The Model 226 Plantar/Tail Stimulator Analgesia Meter (IITC, Woodland Hills, CA) is used to apply a radiant heat beam from underneath the glass platform to the plantar surface of the hind paws. During all test trials, the idle intensity and active intensity of the heat

source are set at 1 and 55 respectively, and a cut off time of 20 seconds is used to prevent tissue damage.

Neuropathic pain model: Spinal Nerve Ligation

[0693] The spinal nerve ligation (SNL) neuropathic pain model is used as an animal (i.e. rat) model of neuropathic pain. In the SNL test, the lumbar roots of spinal nerves L5 and L6 are tightly ligated to cause nerve injury, which results in the development of mechanical hyperalgesia, mechanical allodynia and thermal hypersensitivity. The surgery is performed two weeks before the test day in order for the pain state to fully develop in the animals. Several spinal nerve ligation variations are used to characterize the analgesic properties of a compound of the invention.

Ligation of the L5 spinal nerve;
Ligation of the L5 and L6 spinal nerves;
Ligation and transection of the L5 spinal nerve;
Ligation and transection of the L5 and L6 spinal nerves; or
Mild irritation of the L4 spinal nerve in combination with any one of the above (1)-(4).

[0694] While the animals are anaesthetized under 3.5% isofluorane delivered via a nose cone, an approximately 2.5 cm longitudinal incision is made using a number 10 scalpel blade in the skin just lateral to the dorsal midline, using the level of the posterior iliac crests as the midpoint of the incision. Following the incision, the isoflourane is readjusted to maintenance levels (1.5% – 2.5%). At mid-sacral region, an incision is made with the scalpel blade, sliding the blade along the side of the vertebral column (in the saggital plane) until the blade hits the sacrum. Scissors tips are introduced through the incision and the muscle and ligaments are removed from the spine to expose 2-3 cm of the vertebral column. The muscle and fascia are cleared from the spinal vertebra in order to locate the point where the nerve exits from the vertebra. A small glass hook is placed medial to the spinal nerves and the spinal nerves are gently elevated from the surrounding tissues. Once the spinal nerves have been isolated, a small length of non-degradable 6-0 sterilized silk thread is wound twice around the ball at the tip of the glass hook and passed back under the nerve. The spinal nerves are then firmly ligated by tying a knot, ensuring that the nerve bulges on both sides of the ligature. The procedure may be repeated as needed. In some animals, the L4 spinal nerve may be lightly rubbed (up to 20 times) with the small glass hook to maximize the development of neuropathic pain. Antibacterial ointment is applied directly into the incision, and the muscle is closed using sterilized sutures. Betadine is applied onto the muscle and its

surroundings, followed by skin closure with surgical staples or sterile non-absorable monofilament 5-0 nylon sutures.

[0695] The analgesic effect produced by topical administration of a compound of the invention to the animals can then be observed by measuring the paw withdrawal threshold of animals to mechanical tactile stimuli. These may be measured using either the mechanical allodynia procedure or the mechanical hyperalgesia procedure as described below. After establishment of the appropriate baseline measurements by either method, topical formulation of a compound of the invention is applied on the ipsilateral ankle and foot. The animals are then placed in plastic tunnels for 15 minutes to prevent them from licking the treated area and removing the compound. Animals are placed in the acrylic enclosure for 15 minutes before testing the ipsilateral paw by either of the methods described below, and the responses are recorded at 0.5, 1.0 and 2.0 hour post treatment.

Mechanical allodynia method

[0696] The pain threshold of animals to mechanical alloydnia for both operated and control animals can be measured approximately 14 days post-surgery using manual calibrated von Frey filaments as follows. Animals are placed in an elevated plexiglass enclosure set on a mire mesh surface. Animals are allowed to acclimate for 20-30 minutes. Pre-calibrated Von Frey hairs are applied perpendicularly to the plantar surface of the ipsilateral paw of the animals starting from the 2.0 g hair, with sufficient force to cause slight buckling of the hair against the paw to establish the baseline measurements. Stimuli are presented in a consecutive manner, either in an ascending or descending order until the first change in response is noted, after which four additional responses are recorded for a total of six responses. The six responses measured in grams are entered into a formula as described by Chaplan, S.R. et al., J. Neurosci. Methods, 1994 Jul;53(1):55-63, and a 50% withdrawal threshold is calculated. This constitutes the mechanical allodynia value.

Mechanical hyperalgesia method

[0697] The response thresholds of animals to tactile stimuli are measured using the Model 2290 Electrovonfrey anesthesiometer (IITC Life Science, Woodland Hills, CA). Animals are placed in an elevated Plexiglas enclosure set on a wire mesh surface. After 15 minutes of accommodation in this enclosure, a von Frey hair is applied perpendicularly to the plantar surface of the ipsilateral hind paws of the animals, with sufficient force, measured in grams, to elicit a crisp response of the paw. A response indicates a withdrawal from the painful stimulus and

constitutes the efficacy endpoint. The data are expressed as percent change from baseline threshold measured in grams.

Example 402: In Vivo Assay for Treatment of Pruritus

[0698] This example describes experimental protocols that can be employed to test efficacy of the compounds disclosed herein.

[0699] The compounds of the invention can be evaluated for their activity as antipruritic agents by in vivo test using rodent models. One established model for peripherally elicited pruritus is through the injection of serotonin into the rostral back area (neck) in hairless rats. Prior to serotonin injections (e.g., 2 mg/mL, 50 μL), a dose of a compound of the present invention can be applied systemically through oral, intravenous or intraperitoneal routes or topically to a circular area fixed diameter (e.g. 18 mm). Following dosing, the serotonin injections are given in the area of the topical dosing. After serotonin injection the animal behaviour is monitored by video recording for 20 min-1.5 h, and the number of scratches in this time compared to vehicle treated animals. Thus, application of a compound of the current invention could suppress serotonin-induced scratching in rats.

Example 403: Cryo-Electron Microscopy Methods

[0700] Crystal structures of NaV1.7 receptors, with inhibitor molecules as described herein, were obtained using cryo-electron microscopy methods.

[0701] Cryo-EM data were processed using a combination of RELION (Scheres, S. H. RELION: implementation of a Bayesian approach to cryo-EM structure determination. *J. Struct. Biol.*, 180, 519-530, doi:10.1016/j.jsb.2012.09.006 (2012)) and cisTEM (Grant, T., Rohou, A. and Grigorieff, N., cisTEM, user-friendly software for single-particle image processing. Elife 7, doi:10.7554/eLife.35383 (2018)) software packages. Movies were corrected for frame motion using relion's MotionCor2 (Zheng, S. Q. et al. MotionCor2: anisotropic correction of beam-induced motion for improved cryo-electron microscopy. *Nat. Methods* 14, 331-332, doi:10.1038/nmeth.4193 (2017)) implementation and contrast-transfer function (CTF) parameters were fit using the 30-4.5 Å band of the spectrum with CTFFIND-4 (Rohou, A. and Grigorieff, N. CTFFIND4: Fast and accurate defocus estimation from electron micrographs. *J. Struct. Biol.* 192, 216-221, doi:10.1016/j.jsb.2015.08.008 (2015)). For example, for the compound of Example 96, 12,339 movies were motion corrected and filtered based on the detected fit resolution better than 6Å. Particles were picked using 30 Å low-pass filtered projections of a NavPas 3D reconstruction as template with gautomatch (https://www2.mrc-lmb.cam.ac.uk/research/locally-developed-

software/zhang-software/#gauto). Particles were sorted during RELION 2D classification and selected particles were imported into cisTEM for 3D refinements. For the compound of Example 96 2,741,402 particles were isolated from the images resulting from movie alignment and subjected to 2D classification, by dividing them into 100 classes. High-resolution reconstructions were obtained after auto- refine and manual refinement with a mask excluding the nanodisc scaffold proteins and by applying low-pass filter outside the mask (filter resolution 20 Å) and a score threshold of 0.1-0.3. For 3D refinement, which at no point used any data at frequencies higher than 3.0-4.0 Å (i.e., 3.0 Å for NaVPas-Example 96), converged to a high resolution map (2.2 Å in the case of NaVPas-Example 96, using a Fourier shell correlation (FSC) = 0.143, determined in cisTEM). For model building and figure preparation, Phenix ResolveCryoEM (Terwilliger T. C., Ludtke S. J., Read R. J., Adams P. D., and Afonine P. V. "Improvement of cryo-EM maps by density modification", bioRxiv (2019)) density modification was applied. Local resolution was determined in cisTEM using an in-house re-implementation of the blocres algorithm (Cardone, G., Heymann, J. B. and Steven, A. C., One number does not fit all: mapping local variations in resolution in cryo-EM reconstructions. *J. Struct. Biol.* 184, 226-236, (2013), doi:10.1016/j.jsb.2013.08.002). FIGs. 9 and 10 illustrate aspects of the CryoEM studies of this example.

[0702] A PDB-file (Protein Databank format) of atom coordinates for VSD-only residues and small organic molecule bound thereto is found in the Appendix to this specification. The structure illustrates an inhibitor molecule bound in a "hybrid" pose relative to previously known binding configurations for prior inhibitor molecules.

[0703] FIGs. 3A, 3B illustrate the "hybrid pose" relative to distinct poses for prior families of NaV1.7 inhibitors, referred to as "aryl" series, and "acyl" series, respectively. It can be seen from these depictions that the binding site comprises two distinct binding regions, approximately at right-angles to one another. One region predominantly accommodates aryl series molecules, whereas the other predominantly fits acyl-series molecules. Based on this understanding, molecules that are "hybrids" or "fusions" or "chimaeras" or molecules having respectively aryl series and acyl series characteristics can be expected to fit simultaneously into both binding regions. Molecules that are able to fit into both binding regions can thereby be expected to have superior binding to molecules that can only fit in one or other of the two binding regions.

[0704] All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non patent publications referred to in this specification are incorporated herein by reference in their entireties.

[0705] Although the foregoing invention has been described in some detail to facilitate understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims. Accordingly, the described embodiments are to be considered as illustrative and not restrictive, and the invention is not to be limited to the details given herein, but may be modified within the scope and equivalents of the appended claims.

APPENDIX

PDB File

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REMARK   3
REMARK   3 REFINEMENT.
REMARK   3  PROGRAM     : PHENIX (1.18.2-3874_final: phenix.real_space_refine)
REMARK   3   AUTHORS     : Adams,Afonine,Bunkoczi,Burnley,Chen,Dar,Davis,
REMARK   3               : Draizen,Echols,Gildea,Gros,Grosse-Kunstleve,Headd,
REMARK   3               : Hintze,Hung,Ioerger,Liebschner,McCoy,McKee,Moriarty,
REMARK   3               : Oeffner,Poon,Read,Richardson,Richardson,Sacchettini,
REMARK   3               : Sauter,Sobolev,Storoni,Terwilliger,Williams,Zwart
REMARK   3
REMARK   3  SCATTERING TABLE: ELECTRON
REMARK   3
REMARK   3  REFINEMENT TARGET: REAL-SPACE (WEIGHTED MAP SUM AT ATOM CENTERS)
REMARK   3
REMARK   3  MODEL TO MAP FIT.
REMARK   3    CC_mask  : 0.7148
REMARK   3    CC_volume: 0.7034
REMARK   3    CC_peaks : 0.5910
REMARK   3
REMARK   3 GEOMETRY RESTRAINTS LIBRARY: GEOSTD + MONOMER LIBRARY + CDL V1.2
REMARK   3 DEVIATIONS FROM IDEAL VALUES.
REMARK   3   BOND      :  0.003   0.047   9826
REMARK   3   ANGLE     :  0.651  11.559  13319
REMARK   3   CHIRALITY :  0.141   1.691   1538
REMARK   3   PLANARITY :  0.003   0.040   1573
REMARK   3   DIHEDRAL  : 27.882 179.999   1451
REMARK   3   MIN NONBONDED DISTANCE : 1.972
REMARK   3
REMARK   3 MOLPROBITY STATISTICS.
REMARK   3   ALL-ATOM CLASHSCORE : 3.38
REMARK   3   RAMACHANDRAN PLOT:
REMARK   3     OUTLIERS :  0.00 %
REMARK   3     ALLOWED  :  2.08 %
REMARK   3     FAVORED  : 97.92 %
REMARK   3   ROTAMER OUTLIERS :  0.30 %
REMARK   3   CBETA DEVIATIONS :  0.00 %
REMARK   3   PEPTIDE PLANE:
REMARK   3     CIS-PROLINE     : 0.00 %
REMARK   3     CIS-GENERAL     : 0.00 %
REMARK   3     TWISTED PROLINE : 0.00 %
REMARK   3     TWISTED GENERAL : 0.00 %
REMARK   3
REMARK   3 RAMA-Z (RAMACHANDRAN PLOT Z-SCORE):
REMARK   3 INTERPRETATION: BAD |RAMA-Z| > 3; SUSPICIOUS 2 < |RAMA-Z| < 3;
GOOD |RAMA-Z| < 2.
REMARK   3 SCORES FOR WHOLE/HELIX/SHEET/LOOP ARE SCALED INDEPENDENTLY;
REMARK   3 THEREFORE, THE VALUES ARE NOT RELATED IN A SIMPLE MANNER.
REMARK   3   WHOLE:  2.10 (0.26), RESIDUES: 1108
REMARK   3   HELIX:  1.96 (0.18), RESIDUES: 821
REMARK   3   SHEET: -3.37 (0.82), RESIDUES: 22
REMARK   3   LOOP :  0.10 (0.41), RESIDUES: 265
REMARK   3
HELIX   38  38 LYS A 1158  VAL A 1167  1                                  10
HELIX   39  39 GLN A 1170  MET A 1188  1                                  19
HELIX   40  40 GLN A 1196  THR A 1230  1                                  35
HELIX   41  41 GLY A 1232  GLU A 1255  1                                  24
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HELIX   42  42 PRO A 1261  ARG A 1274  1                                      14
HELIX   43  43 LEU A 1276  VAL A 1279  5                                       4
HELIX   44  44 LYS A 1283  LYS A 1294  1                                      12
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SCALE2      0.000000  0.008463  0.000000        0.00000
SCALE3      0.000000  0.000000  0.009944        0.00000
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ATOM  13797  CA  LYS A1158     110.480 187.597 163.308  1.00 29.10           C
ATOM  13798  C   LYS A1158     111.535 187.438 164.396  1.00 29.10           C
ATOM  13799  O   LYS A1158     112.648 187.961 164.277  1.00 29.10           O
ATOM  13800  CB  LYS A1158     109.393 188.577 163.754  1.00 29.10           C
ATOM  13801  H   LYS A1158     109.032 186.265 163.101  1.00 29.10           H
ATOM  13802  HA  LYS A1158     110.913 187.968 162.523  1.00 29.10           H
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ATOM  13804  CA  ILE A1159     112.138 186.575 166.582  1.00 28.02           C
ATOM  13805  C   ILE A1159     113.352 185.754 166.163  1.00 28.02           C
ATOM  13806  O   ILE A1159     114.504 186.142 166.404  1.00 28.02           O
ATOM  13807  CB  ILE A1159     111.427 185.951 167.798  1.00 28.02           C
ATOM  13808  CG1 ILE A1159     110.374 186.915 168.353  1.00 28.02           C
ATOM  13809  CG2 ILE A1159     112.437 185.582 168.879  1.00 28.02           C
ATOM  13810  CD1 ILE A1159     108.988 186.717 167.771  1.00 28.02           C
ATOM  13811  H   ILE A1159     110.463 186.290 165.564  1.00 28.02           H
ATOM  13812  HA  ILE A1159     112.451 187.456 166.839  1.00 28.02           H
ATOM  13813  HB  ILE A1159     110.979 185.141 167.508  1.00 28.02           H
ATOM  13814 HG12 ILE A1159     110.308 186.794 169.313  1.00 28.02           H
ATOM  13815 HG13 ILE A1159     110.648 187.825 168.157  1.00 28.02           H
ATOM  13816 HG21 ILE A1159     111.963 185.392 169.704  1.00 28.02           H
ATOM  13817 HG22 ILE A1159     112.932 184.796 168.600  1.00 28.02           H
ATOM  13818 HG23 ILE A1159     113.044 186.327 169.013  1.00 28.02           H
ATOM  13819 HD11 ILE A1159     108.367 187.302 168.233  1.00 28.02           H
ATOM  13820 HD12 ILE A1159     109.003 186.935 166.826  1.00 28.02           H
ATOM  13821 HD13 ILE A1159     108.724 185.792 167.894  1.00 28.02           H
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ATOM  13831  H   GLN A1160     112.331 184.292 165.351  1.00 25.91           H
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ATOM  13838 HE22 GLN A1160     112.999 178.392 164.964  1.00 25.91           H
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ATOM  13850  CB  CYS A1162     115.420 189.529 165.453  1.00 27.46        C
ATOM  13851  SG  CYS A1162     116.360 190.460 166.685  1.00 27.46        S
ATOM  13852  H   CYS A1162     114.686 187.663 164.076  1.00 27.46        H
ATOM  13853  HA  CYS A1162     116.615 189.404 163.795  1.00 27.46        H
ATOM  13854  HB2 CYS A1162     114.862 190.159 164.970  1.00 27.46        H
ATOM  13855  HB3 CYS A1162     114.860 188.894 165.927  1.00 27.46        H
ATOM  13856  HG  CYS A1162     115.593 191.009 167.427  1.00 27.46        H
ATOM  13857  N   ILE A1163     117.274 187.000 165.812  1.00 23.24        N
ATOM  13858  CA  ILE A1163     118.392 186.317 166.459  1.00 23.24        C
ATOM  13859  C   ILE A1163     119.401 185.855 165.412  1.00 23.24        C
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ATOM  13865  H   ILE A1163     116.511 186.613 165.903  1.00 23.24        H
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ATOM  13875 HD13 ILE A1163     117.169 184.244 169.921  1.00 23.24        H
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ATOM  13889  HB2 PHE A1164     118.213 183.974 162.352  1.00 23.58        H
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ATOM  13905  HA  ASP A1165     121.260 188.342 161.290  1.00 24.66        H
ATOM  13906  HB2 ASP A1165     119.269 189.839 162.621  1.00 24.66        H
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ATOM  13911  O   LEU A1166     124.631 188.640 166.020  1.00 23.50           O
ATOM  13912  CB  LEU A1166     121.608 189.308 166.842  1.00 23.50           C
ATOM  13913  CG  LEU A1166     121.110 190.701 167.230  1.00 23.50           C
ATOM  13914  CD1 LEU A1166     119.873 190.600 168.109  1.00 23.50           C
ATOM  13915  CD2 LEU A1166     122.206 191.488 167.931  1.00 23.50           C
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ATOM  13918  HB2 LEU A1166     120.834 188.725 166.798  1.00 23.50           H
ATOM  13919  HB3 LEU A1166     122.198 189.004 167.550  1.00 23.50           H
ATOM  13920  HG  LEU A1166     120.865 191.183 166.425  1.00 23.50           H
ATOM  13921 HD11 LEU A1166     119.575 191.495 168.338  1.00 23.50           H
ATOM  13922 HD12 LEU A1166     119.177 190.134 167.622  1.00 23.50           H
ATOM  13923 HD13 LEU A1166     120.099 190.110 168.915  1.00 23.50           H
ATOM  13924 HD21 LEU A1166     121.841 192.332 168.239  1.00 23.50           H
ATOM  13925 HD22 LEU A1166     122.531 190.973 168.687  1.00 23.50           H
ATOM  13926 HD23 LEU A1166     122.929 191.649 167.305  1.00 23.50           H
ATOM  13927  N   VAL A1167     123.301 186.952 165.354  1.00 20.50           N
ATOM  13928  CA  VAL A1167     124.310 185.931 165.619  1.00 20.50           C
ATOM  13929  C   VAL A1167     125.281 185.728 164.459  1.00 20.50           C
ATOM  13930  O   VAL A1167     126.412 185.273 164.684  1.00 20.50           O
ATOM  13931  CB  VAL A1167     123.621 184.600 165.977  1.00 20.50           C
ATOM  13932  CG1 VAL A1167     124.530 183.404 165.691  1.00 20.50           C
ATOM  13933  CG2 VAL A1167     123.186 184.607 167.435  1.00 20.50           C
ATOM  13934  H   VAL A1167     122.576 186.651 165.002  1.00 20.50           H
ATOM  13935  HA  VAL A1167     124.831 186.206 166.390  1.00 20.50           H
ATOM  13936  HB  VAL A1167     122.825 184.504 165.431  1.00 20.50           H
ATOM  13937 HG11 VAL A1167     124.153 182.621 166.124  1.00 20.50           H
ATOM  13938 HG12 VAL A1167     124.578 183.252 164.734  1.00 20.50           H
ATOM  13939 HG13 VAL A1167     125.413 183.578 166.051  1.00 20.50           H
ATOM  13940 HG21 VAL A1167     122.777 183.754 167.648  1.00 20.50           H
ATOM  13941 HG22 VAL A1167     123.965 184.749 167.996  1.00 20.50           H
ATOM  13942 HG23 VAL A1167     122.547 185.324 167.570  1.00 20.50           H
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ATOM  13944  CA  THR A1168     125.692 185.793 162.046  1.00 22.64           C
ATOM  13945  C   THR A1168     126.568 186.975 161.640  1.00 22.64           C
ATOM  13946  O   THR A1168     126.834 187.160 160.445  1.00 22.64           O
ATOM  13947  CB  THR A1168     124.790 185.383 160.881  1.00 22.64           C
ATOM  13948  OG1 THR A1168     123.842 186.425 160.615  1.00 22.64           O
ATOM  13949  CG2 THR A1168     124.049 184.093 161.204  1.00 22.64           C
ATOM  13950  H   THR A1168     124.140 186.458 163.057  1.00 22.64           H
ATOM  13951  HA  THR A1168     126.281 185.046 162.237  1.00 22.64           H
ATOM  13952  HB  THR A1168     125.332 185.233 160.091  1.00 22.64           H
ATOM  13953  HG1 THR A1168     123.336 186.530 161.277  1.00 22.64           H
ATOM  13954 HG21 THR A1168     123.508 183.823 160.445  1.00 22.64           H
ATOM  13955 HG22 THR A1168     124.684 183.388 161.403  1.00 22.64           H
ATOM  13956 HG23 THR A1168     123.472 184.224 161.972  1.00 22.64           H
ATOM  13957  N   ASN A1169     127.023 187.778 162.597  1.00 25.59           N
ATOM  13958  CA  ASN A1169     127.870 188.929 162.324  1.00 25.59           C
ATOM  13959  C   ASN A1169     129.243 188.741 162.959  1.00 25.59           C
ATOM  13960  O   ASN A1169     129.413 187.986 163.919  1.00 25.59           O
ATOM  13961  CB  ASN A1169     127.223 190.218 162.844  1.00 25.59           C
ATOM  13962  CG  ASN A1169     127.877 191.465 162.283  1.00 25.59           C
ATOM  13963  OD1 ASN A1169     128.396 191.460 161.167  1.00 25.59           O
ATOM  13964  ND2 ASN A1169     127.850 192.545 163.055  1.00 25.59           N
ATOM  13965  H   ASN A1169     126.850 187.671 163.433  1.00 25.59           H
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ATOM  13966  HA  ASN A1169     127.992 189.019 161.366  1.00 25.59        H
ATOM  13967  HB2 ASN A1169     126.288 190.228 162.588  1.00 25.59        H
ATOM  13968  HB3 ASN A1169     127.304 190.245 163.810  1.00 25.59        H
ATOM  13969 HD21 ASN A1169     127.477 192.512 163.829  1.00 25.59        H
ATOM  13970 HD22 ASN A1169     128.207 193.278 162.781  1.00 25.59        H
ATOM  13971  N   GLN A1170     130.231 189.448 162.400  1.00 25.54        N
ATOM  13972  CA  GLN A1170     131.598 189.341 162.901  1.00 25.54        C
ATOM  13973  C   GLN A1170     131.706 189.808 164.347  1.00 25.54        C
ATOM  13974  O   GLN A1170     132.553 189.309 165.100  1.00 25.54        O
ATOM  13975  CB  GLN A1170     132.544 190.157 162.018  1.00 25.54        C
ATOM  13976  CG  GLN A1170     132.659 189.656 160.587  1.00 25.54        C
ATOM  13977  CD  GLN A1170     133.224 188.253 160.500  1.00 25.54        C
ATOM  13978  OE1 GLN A1170     134.136 187.891 161.244  1.00 25.54        O
ATOM  13979  NE2 GLN A1170     132.688 187.454 159.585  1.00 25.54        N
ATOM  13980  H   GLN A1170     130.134 189.989 161.739  1.00 25.54        H
ATOM  13981  HA  GLN A1170     131.876 188.412 162.866  1.00 25.54        H
ATOM  13982  HB2 GLN A1170     132.224 191.072 161.985  1.00 25.54        H
ATOM  13983  HB3 GLN A1170     133.431 190.134 162.410  1.00 25.54        H
ATOM  13984  HG2 GLN A1170     131.777 189.650 160.182  1.00 25.54        H
ATOM  13985  HG3 GLN A1170     133.247 190.248 160.092  1.00 25.54        H
ATOM  13986 HE21 GLN A1170     132.052 187.743 159.082  1.00 25.54        H
ATOM  13987 HE22 GLN A1170     132.974 186.649 159.495  1.00 25.54        H
ATOM  13988  N   ALA A1171     130.866 190.764 164.749  1.00 21.39        N
ATOM  13989  CA  ALA A1171     130.940 191.289 166.108  1.00 21.39        C
ATOM  13990  C   ALA A1171     130.718 190.189 167.136  1.00 21.39        C
ATOM  13991  O   ALA A1171     131.395 190.149 168.169  1.00 21.39        O
ATOM  13992  CB  ALA A1171     129.917 192.409 166.292  1.00 21.39        C
ATOM  13993  H   ALA A1171     130.254 191.119 164.261  1.00 21.39        H
ATOM  13994  HA  ALA A1171     131.824 191.663 166.254  1.00 21.39        H
ATOM  13995  HB1 ALA A1171     129.979 192.747 167.199  1.00 21.39        H
ATOM  13996  HB2 ALA A1171     130.110 193.120 165.660  1.00 21.39        H
ATOM  13997  HB3 ALA A1171     129.029 192.055 166.130  1.00 21.39        H
ATOM  13998  N   PHE A1172     129.771 189.287 166.872  1.00 17.35        N
ATOM  13999  CA  PHE A1172     129.500 188.197 167.804  1.00 17.35        C
ATOM  14000  C   PHE A1172     130.732 187.318 167.994  1.00 17.35        C
ATOM  14001  O   PHE A1172     131.119 187.001 169.127  1.00 17.35        O
ATOM  14002  CB  PHE A1172     128.318 187.373 167.292  1.00 17.35        C
ATOM  14003  CG  PHE A1172     127.697 186.486 168.331  1.00 17.35        C
ATOM  14004  CD1 PHE A1172     126.917 187.021 169.341  1.00 17.35        C
ATOM  14005  CD2 PHE A1172     127.882 185.115 168.288  1.00 17.35        C
ATOM  14006  CE1 PHE A1172     126.342 186.205 170.296  1.00 17.35        C
ATOM  14007  CE2 PHE A1172     127.309 184.295 169.238  1.00 17.35        C
ATOM  14008  CZ  PHE A1172     126.538 184.841 170.244  1.00 17.35        C
ATOM  14009  H   PHE A1172     129.278 189.285 166.167  1.00 17.35        H
ATOM  14010  HA  PHE A1172     129.258 188.569 168.666  1.00 17.35        H
ATOM  14011  HB2 PHE A1172     127.631 187.978 166.971  1.00 17.35        H
ATOM  14012  HB3 PHE A1172     128.623 186.808 166.565  1.00 17.35        H
ATOM  14013  HD1 PHE A1172     126.783 187.941 169.381  1.00 17.35        H
ATOM  14014  HD2 PHE A1172     128.402 184.742 167.613  1.00 17.35        H
ATOM  14015  HE1 PHE A1172     125.822 186.575 170.972  1.00 17.35        H
ATOM  14016  HE2 PHE A1172     127.443 183.375 169.201  1.00 17.35        H
ATOM  14017  HZ  PHE A1172     126.151 184.289 170.885  1.00 17.35        H
ATOM  14018  N   ASP A1173     131.370 186.920 166.891  1.00 18.37        N
ATOM  14019  CA  ASP A1173     132.546 186.062 166.986  1.00 18.37        C
ATOM  14020  C   ASP A1173     133.692 186.773 167.695  1.00 18.37        C
ATOM  14021  O   ASP A1173     134.392 186.173 168.521  1.00 18.37        O
ATOM  14022  CB  ASP A1173     132.979 185.610 165.591  1.00 18.37        C
ATOM  14023  CG  ASP A1173     131.837 185.018 164.789  1.00 18.37        C
ATOM  14024  OD1 ASP A1173     130.666 185.284 165.133  1.00 18.37        O
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ATOM  14025  OD2 ASP A1173     132.110 184.287 163.814  1.00 18.37           O
ATOM  14026  H   ASP A1173     131.143 187.132 166.088  1.00 18.37           H
ATOM  14027  HA  ASP A1173     132.320 185.271 167.501  1.00 18.37           H
ATOM  14028  HB2 ASP A1173     133.323 186.375 165.104  1.00 18.37           H
ATOM  14029  HB3 ASP A1173     133.668 184.933 165.677  1.00 18.37           H
ATOM  14030  N   ILE A1174     133.905 188.053 167.380  1.00 15.56           N
ATOM  14031  CA  ILE A1174     134.981 188.798 168.029  1.00 15.56           C
ATOM  14032  C   ILE A1174     134.714 188.913 169.525  1.00 15.56           C
ATOM  14033  O   ILE A1174     135.635 188.815 170.345  1.00 15.56           O
ATOM  14034  CB  ILE A1174     135.152 190.177 167.364  1.00 15.56           C
ATOM  14035  CG1 ILE A1174     135.657 189.992 165.926  1.00 15.56           C
ATOM  14036  CG2 ILE A1174     136.101 191.064 168.184  1.00 15.56           C
ATOM  14037  CD1 ILE A1174     136.448 191.159 165.361  1.00 15.56           C
ATOM  14038  H   ILE A1174     133.451 188.504 166.806  1.00 15.56           H
ATOM  14039  HA  ILE A1174     135.811 188.309 167.916  1.00 15.56           H
ATOM  14040  HB  ILE A1174     134.284 190.609 167.330  1.00 15.56           H
ATOM  14041 HG12 ILE A1174     136.231 189.211 165.897  1.00 15.56           H
ATOM  14042 HG13 ILE A1174     134.892 189.852 165.346  1.00 15.56           H
ATOM  14043 HG21 ILE A1174     136.160 191.941 167.774  1.00 15.56           H
ATOM  14044 HG22 ILE A1174     135.760 191.166 169.086  1.00 15.56           H
ATOM  14045 HG23 ILE A1174     136.978 190.650 168.207  1.00 15.56           H
ATOM  14046 HD11 ILE A1174     136.568 191.024 164.408  1.00 15.56           H
ATOM  14047 HD12 ILE A1174     135.956 191.980 165.518  1.00 15.56           H
ATOM  14048 HD13 ILE A1174     137.312 191.200 165.799  1.00 15.56           H
ATOM  14049  N   SER A1175     133.452 189.126 169.905  1.00 13.45           N
ATOM  14050  CA  SER A1175     133.108 189.200 171.321  1.00 13.45           C
ATOM  14051  C   SER A1175     133.358 187.869 172.017  1.00 13.45           C
ATOM  14052  O   SER A1175     133.837 187.836 173.157  1.00 13.45           O
ATOM  14053  CB  SER A1175     131.649 189.625 171.480  1.00 13.45           C
ATOM  14054  OG  SER A1175     131.338 190.703 170.616  1.00 13.45           O
ATOM  14055  H   SER A1175     132.787 189.228 169.369  1.00 13.45           H
ATOM  14056  HA  SER A1175     133.665 189.871 171.746  1.00 13.45           H
ATOM  14057  HB2 SER A1175     131.076 188.872 171.265  1.00 13.45           H
ATOM  14058  HB3 SER A1175     131.500 189.902 172.398  1.00 13.45           H
ATOM  14059  HG  SER A1175     131.837 191.358 170.783  1.00 13.45           H
ATOM  14060  N   ILE A1176     133.029 186.759 171.354  1.00  9.36           N
ATOM  14061  CA  ILE A1176     133.299 185.447 171.941  1.00  9.36           C
ATOM  14062  C   ILE A1176     134.798 185.251 172.137  1.00  9.36           C
ATOM  14063  O   ILE A1176     135.245 184.735 173.170  1.00  9.36           O
ATOM  14064  CB  ILE A1176     132.689 184.331 171.071  1.00  9.36           C
ATOM  14065  CG1 ILE A1176     131.160 184.441 171.039  1.00  9.36           C
ATOM  14066  CG2 ILE A1176     133.116 182.962 171.582  1.00  9.36           C
ATOM  14067  CD1 ILE A1176     130.490 184.330 172.398  1.00  9.36           C
ATOM  14068  H   ILE A1176     132.656 186.737 170.579  1.00  9.36           H
ATOM  14069  HA  ILE A1176     132.887 185.407 172.818  1.00  9.36           H
ATOM  14070  HB  ILE A1176     133.021 184.436 170.165  1.00  9.36           H
ATOM  14071 HG12 ILE A1176     130.917 185.301 170.668  1.00  9.36           H
ATOM  14072 HG13 ILE A1176     130.809 183.732 170.478  1.00  9.36           H
ATOM  14073 HG21 ILE A1176     132.527 182.289 171.206  1.00  9.36           H
ATOM  14074 HG22 ILE A1176     134.030 182.791 171.307  1.00  9.36           H
ATOM  14075 HG23 ILE A1176     133.052 182.953 172.550  1.00  9.36           H
ATOM  14076 HD11 ILE A1176     129.531 184.271 172.270  1.00  9.36           H
ATOM  14077 HD12 ILE A1176     130.811 183.533 172.849  1.00  9.36           H
ATOM  14078 HD13 ILE A1176     130.703 185.116 172.924  1.00  9.36           H
ATOM  14079  N   MET A1177     135.599 185.652 171.146  1.00 12.43           N
ATOM  14080  CA  MET A1177     137.050 185.549 171.286  1.00 12.43           C
ATOM  14081  C   MET A1177     137.552 186.395 172.452  1.00 12.43           C
ATOM  14082  O   MET A1177     138.422 185.962 173.220  1.00 12.43           O
ATOM  14083  CB  MET A1177     137.735 185.976 169.986  1.00 12.43           C
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ATOM  14084  CG  MET A1177     137.323 185.171 168.760  1.00 12.43           C
ATOM  14085  SD  MET A1177     138.314 183.682 168.529  1.00 12.43           S
ATOM  14086  CE  MET A1177     137.257 182.449 169.281  1.00 12.43           C
ATOM  14087  H   MET A1177     135.332 185.981 170.398  1.00 12.43           H
ATOM  14088  HA  MET A1177     137.282 184.622 171.452  1.00 12.43           H
ATOM  14089  HB2 MET A1177     137.520 186.906 169.814  1.00 12.43           H
ATOM  14090  HB3 MET A1177     138.693 185.876 170.095  1.00 12.43           H
ATOM  14091  HG2 MET A1177     136.398 184.898 168.854  1.00 12.43           H
ATOM  14092  HG3 MET A1177     137.427 185.725 167.971  1.00 12.43           H
ATOM  14093  HE1 MET A1177     137.683 181.580 169.205  1.00 12.43           H
ATOM  14094  HE2 MET A1177     137.127 182.673 170.215  1.00 12.43           H
ATOM  14095  HE3 MET A1177     136.404 182.441 168.820  1.00 12.43           H
ATOM  14096  N   VAL A1178     137.018 187.610 172.595  1.00  7.81           N
ATOM  14097  CA  VAL A1178     137.426 188.480 173.695  1.00  7.81           C
ATOM  14098  C   VAL A1178     137.065 187.846 175.033  1.00  7.81           C
ATOM  14099  O   VAL A1178     137.838 187.907 175.997  1.00  7.81           O
ATOM  14100  CB  VAL A1178     136.786 189.872 173.535  1.00  7.81           C
ATOM  14101  CG1 VAL A1178     136.852 190.648 174.844  1.00  7.81           C
ATOM  14102  CG2 VAL A1178     137.465 190.642 172.412  1.00  7.81           C
ATOM  14103  H   VAL A1178     136.424 187.949 172.073  1.00  7.81           H
ATOM  14104  HA  VAL A1178     138.389 188.590 173.668  1.00  7.81           H
ATOM  14105  HB  VAL A1178     135.851 189.763 173.300  1.00  7.81           H
ATOM  14106 HG11 VAL A1178     136.714 191.590 174.656  1.00  7.81           H
ATOM  14107 HG12 VAL A1178     136.159 190.327 175.442  1.00  7.81           H
ATOM  14108 HG13 VAL A1178     137.726 190.518 175.245  1.00  7.81           H
ATOM  14109 HG21 VAL A1178     137.034 191.505 172.315  1.00  7.81           H
ATOM  14110 HG22 VAL A1178     138.402 190.762 172.634  1.00  7.81           H
ATOM  14111 HG23 VAL A1178     137.383 190.135 171.589  1.00  7.81           H
ATOM  14112  N   LEU A1179     135.878 187.243 175.117  1.00  6.70           N
ATOM  14113  CA  LEU A1179     135.474 186.571 176.348  1.00  6.70           C
ATOM  14114  C   LEU A1179     136.403 185.408 176.669  1.00  6.70           C
ATOM  14115  O   LEU A1179     136.751 185.182 177.834  1.00  6.70           O
ATOM  14116  CB  LEU A1179     134.030 186.083 176.230  1.00  6.70           C
ATOM  14117  CG  LEU A1179     132.941 187.153 176.336  1.00  6.70           C
ATOM  14118  CD1 LEU A1179     131.585 186.564 175.980  1.00  6.70           C
ATOM  14119  CD2 LEU A1179     132.911 187.764 177.729  1.00  6.70           C
ATOM  14120  H   LEU A1179     135.297 187.208 174.484  1.00  6.70           H
ATOM  14121  HA  LEU A1179     135.522 187.203 177.083  1.00  6.70           H
ATOM  14122  HB2 LEU A1179     133.926 185.651 175.368  1.00  6.70           H
ATOM  14123  HB3 LEU A1179     133.869 185.437 176.935  1.00  6.70           H
ATOM  14124  HG  LEU A1179     133.135 187.862 175.703  1.00  6.70           H
ATOM  14125 HD11 LEU A1179     130.918 187.267 176.010  1.00  6.70           H
ATOM  14126 HD12 LEU A1179     131.630 186.187 175.087  1.00  6.70           H
ATOM  14127 HD13 LEU A1179     131.365 185.870 176.621  1.00  6.70           H
ATOM  14128 HD21 LEU A1179     132.122 188.322 177.811  1.00  6.70           H
ATOM  14129 HD22 LEU A1179     132.882 187.051 178.386  1.00  6.70           H
ATOM  14130 HD23 LEU A1179     133.709 188.300 177.858  1.00  6.70           H
ATOM  14131  N   ILE A1180     136.804 184.648 175.648  1.00  6.90           N
ATOM  14132  CA  ILE A1180     137.742 183.549 175.871  1.00  6.90           C
ATOM  14133  C   ILE A1180     139.068 184.082 176.400  1.00  6.90           C
ATOM  14134  O   ILE A1180     139.663 183.509 177.322  1.00  6.90           O
ATOM  14135  CB  ILE A1180     137.934 182.739 174.575  1.00  6.90           C
ATOM  14136  CG1 ILE A1180     136.653 181.978 174.232  1.00  6.90           C
ATOM  14137  CG2 ILE A1180     139.102 181.774 174.718  1.00  6.90           C
ATOM  14138  CD1 ILE A1180     136.462 181.749 172.753  1.00  6.90           C
ATOM  14139  H   ILE A1180     136.553 184.746 174.831  1.00  6.90           H
ATOM  14140  HA  ILE A1180     137.371 182.954 176.541  1.00  6.90           H
ATOM  14141  HB  ILE A1180     138.130 183.356 173.853  1.00  6.90           H
ATOM  14142 HG12 ILE A1180     136.679 181.111 174.665  1.00  6.90           H
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ATOM  14143 HG13 ILE A1180     135.890 182.483 174.554  1.00  6.90           H
ATOM  14144 HG21 ILE A1180     139.032 181.092 174.032  1.00  6.90           H
ATOM  14145 HG22 ILE A1180     139.934 182.262 174.612  1.00  6.90           H
ATOM  14146 HG23 ILE A1180     139.067 181.363 175.596  1.00  6.90           H
ATOM  14147 HD11 ILE A1180     135.709 181.152 172.621  1.00  6.90           H
ATOM  14148 HD12 ILE A1180     136.287 182.601 172.323  1.00  6.90           H
ATOM  14149 HD13 ILE A1180     137.268 181.352 172.389  1.00  6.90           H
ATOM  14150  N   CYS A1181     139.555 185.181 175.820  1.00  8.30           N
ATOM  14151  CA  CYS A1181     140.802 185.772 176.300  1.00  8.30           C
ATOM  14152  C   CYS A1181     140.672 186.229 177.749  1.00  8.30           C
ATOM  14153  O   CYS A1181     141.591 186.039 178.557  1.00  8.30           O
ATOM  14154  CB  CYS A1181     141.207 186.943 175.407  1.00  8.30           C
ATOM  14155  SG  CYS A1181     141.647 186.475 173.719  1.00  8.30           S
ATOM  14156  H   CYS A1181     139.191 185.595 175.160  1.00  8.30           H
ATOM  14157  HA  CYS A1181     141.505 185.104 176.259  1.00  8.30           H
ATOM  14158  HB2 CYS A1181     140.465 187.566 175.356  1.00  8.30           H
ATOM  14159  HB3 CYS A1181     141.977 187.383 175.801  1.00  8.30           H
ATOM  14160  HG  CYS A1181     141.941 187.466 173.109  1.00  8.30           H
ATOM  14161  N   LEU A1182     139.539 186.844 178.093  1.00  5.89           N
ATOM  14162  CA  LEU A1182     139.325 187.286 179.467  1.00  5.89           C
ATOM  14163  C   LEU A1182     139.296 186.101 180.425  1.00  5.89           C
ATOM  14164  O   LEU A1182     139.847 186.170 181.530  1.00  5.89           O
ATOM  14165  CB  LEU A1182     138.025 188.083 179.561  1.00  5.89           C
ATOM  14166  CG  LEU A1182     138.104 189.538 179.095  1.00  5.89           C
ATOM  14167  CD1 LEU A1182     136.714 190.152 179.044  1.00  5.89           C
ATOM  14168  CD2 LEU A1182     139.021 190.350 179.997  1.00  5.89           C
ATOM  14169  H   LEU A1182     138.889 187.016 177.557  1.00  5.89           H
ATOM  14170  HA  LEU A1182     140.058 187.865 179.728  1.00  5.89           H
ATOM  14171  HB2 LEU A1182     137.353 187.640 179.020  1.00  5.89           H
ATOM  14172  HB3 LEU A1182     137.738 188.091 180.488  1.00  5.89           H
ATOM  14173  HG  LEU A1182     138.472 189.559 178.199  1.00  5.89           H
ATOM  14174 HD11 LEU A1182     136.780 191.052 178.688  1.00  5.89           H
ATOM  14175 HD12 LEU A1182     136.152 189.609 178.469  1.00  5.89           H
ATOM  14176 HD13 LEU A1182     136.346 190.176 179.941  1.00  5.89           H
ATOM  14177 HD21 LEU A1182     138.913 191.292 179.791  1.00  5.89           H
ATOM  14178 HD22 LEU A1182     138.781 190.184 180.922  1.00  5.89           H
ATOM  14179 HD23 LEU A1182     139.939 190.081 179.841  1.00  5.89           H
ATOM  14180  N   ASN A1183     138.650 185.005 180.020  1.00  4.91           N
ATOM  14181  CA  ASN A1183     138.626 183.815 180.865  1.00  4.91           C
ATOM  14182  C   ASN A1183     140.027 183.248 181.051  1.00  4.91           C
ATOM  14183  O   ASN A1183     140.383 182.793 182.145  1.00  4.91           O
ATOM  14184  CB  ASN A1183     137.697 182.760 180.262  1.00  4.91           C
ATOM  14185  CG  ASN A1183     137.281 181.679 181.266  1.00  4.91           C
ATOM  14186  OD1 ASN A1183     136.591 180.728 180.900  1.00  4.91           O
ATOM  14187  ND2 ASN A1183     137.702 181.812 182.524  1.00  4.91           N
ATOM  14188  H   ASN A1183     138.229 184.928 179.274  1.00  4.91           H
ATOM  14189  HA  ASN A1183     138.281 184.078 181.731  1.00  4.91           H
ATOM  14190  HB2 ASN A1183     136.895 183.198 179.937  1.00  4.91           H
ATOM  14191  HB3 ASN A1183     138.155 182.323 179.527  1.00  4.91           H
ATOM  14192 HD21 ASN A1183     137.482 181.216 183.103  1.00  4.91           H
ATOM  14193 HD22 ASN A1183     138.186 182.477 182.768  1.00  4.91           H
ATOM  14194  N   MET A1184     140.836 183.256 179.990  1.00  4.33           N
ATOM  14195  CA  MET A1184     142.220 182.808 180.117  1.00  4.33           C
ATOM  14196  C   MET A1184     142.990 183.683 181.098  1.00  4.33           C
ATOM  14197  O   MET A1184     143.746 183.178 181.939  1.00  4.33           O
ATOM  14198  CB  MET A1184     142.900 182.817 178.749  1.00  4.33           C
ATOM  14199  CG  MET A1184     143.789 181.617 178.498  1.00  4.33           C
ATOM  14200  SD  MET A1184     144.439 181.580 176.818  1.00  4.33           S
ATOM  14201  CE  MET A1184     146.109 181.006 177.114  1.00  4.33           C
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ATOM  14202  H   MET A1184     140.611 183.511 179.200  1.00  4.33           H
ATOM  14203  HA  MET A1184     142.223 181.895 180.445  1.00  4.33           H
ATOM  14204  HB2 MET A1184     142.219 182.828 178.059  1.00  4.33           H
ATOM  14205  HB3 MET A1184     143.450 183.612 178.679  1.00  4.33           H
ATOM  14206  HG2 MET A1184     144.541 181.648 179.110  1.00  4.33           H
ATOM  14207  HG3 MET A1184     143.276 180.809 178.646  1.00  4.33           H
ATOM  14208  HE1 MET A1184     146.575 180.940 176.266  1.00  4.33           H
ATOM  14209  HE2 MET A1184     146.562 181.639 177.693  1.00  4.33           H
ATOM  14210  HE3 MET A1184     146.071 180.136 177.540  1.00  4.33           H
ATOM  14211  N   VAL A1185     142.809 185.002 181.007  1.00  5.28           N
ATOM  14212  CA  VAL A1185     143.482 185.905 181.936  1.00  5.28           C
ATOM  14213  C   VAL A1185     143.052 185.603 183.365  1.00  5.28           C
ATOM  14214  O   VAL A1185     143.874 185.594 184.290  1.00  5.28           O
ATOM  14215  CB  VAL A1185     143.203 187.371 181.557  1.00  5.28           C
ATOM  14216  CG1 VAL A1185     143.555 188.299 182.713  1.00  5.28           C
ATOM  14217  CG2 VAL A1185     143.978 187.751 180.306  1.00  5.28           C
ATOM  14218  H   VAL A1185     142.309 185.392 180.426  1.00  5.28           H
ATOM  14219  HA  VAL A1185     144.440 185.760 181.877  1.00  5.28           H
ATOM  14220  HB  VAL A1185     142.257 187.473 181.367  1.00  5.28           H
ATOM  14221 HG11 VAL A1185     143.646 189.203 182.373  1.00  5.28           H
ATOM  14222 HG12 VAL A1185     142.848 188.268 183.376  1.00  5.28           H
ATOM  14223 HG13 VAL A1185     144.394 188.010 183.105  1.00  5.28           H
ATOM  14224 HG21 VAL A1185     143.792 188.678 180.089  1.00  5.28           H
ATOM  14225 HG22 VAL A1185     144.926 187.635 180.475  1.00  5.28           H
ATOM  14226 HG23 VAL A1185     143.700 187.178 179.575  1.00  5.28           H
ATOM  14227  N   THR A1186     141.758 185.350 183.568  1.00  4.79           N
ATOM  14228  CA  THR A1186     141.277 184.983 184.897  1.00  4.79           C
ATOM  14229  C   THR A1186     141.941 183.701 185.382  1.00  4.79           C
ATOM  14230  O   THR A1186     142.314 183.590 186.556  1.00  4.79           O
ATOM  14231  CB  THR A1186     139.756 184.821 184.880  1.00  4.79           C
ATOM  14232  OG1 THR A1186     139.150 186.002 184.341  1.00  4.79           O
ATOM  14233  CG2 THR A1186     139.223 184.573 186.287  1.00  4.79           C
ATOM  14234  H   THR A1186     141.148 185.383 182.963  1.00  4.79           H
ATOM  14235  HA  THR A1186     141.498 185.692 185.521  1.00  4.79           H
ATOM  14236  HB  THR A1186     139.521 184.059 184.327  1.00  4.79           H
ATOM  14237  HG1 THR A1186     139.346 186.667 184.815  1.00  4.79           H
ATOM  14238 HG21 THR A1186     138.254 184.595 186.281  1.00  4.79           H
ATOM  14239 HG22 THR A1186     139.515 183.706 186.608  1.00  4.79           H
ATOM  14240 HG23 THR A1186     139.549 185.260 186.890  1.00  4.79           H
ATOM  14241  N   MET A1187     142.093 182.719 184.492  1.00  4.25           N
ATOM  14242  CA  MET A1187     142.759 181.477 184.871  1.00  4.25           C
ATOM  14243  C   MET A1187     144.206 181.731 185.274  1.00  4.25           C
ATOM  14244  O   MET A1187     144.735 181.066 186.172  1.00  4.25           O
ATOM  14245  CB  MET A1187     142.699 180.475 183.718  1.00  4.25           C
ATOM  14246  CG  MET A1187     141.366 179.764 183.581  1.00  4.25           C
ATOM  14247  SD  MET A1187     141.511 178.217 182.668  1.00  4.25           S
ATOM  14248  CE  MET A1187     139.921 178.161 181.847  1.00  4.25           C
ATOM  14249  H   MET A1187     141.823 182.747 183.676  1.00  4.25           H
ATOM  14250  HA  MET A1187     142.289 181.091 185.625  1.00  4.25           H
ATOM  14251  HB2 MET A1187     142.870 180.946 182.888  1.00  4.25           H
ATOM  14252  HB3 MET A1187     143.382 179.800 183.858  1.00  4.25           H
ATOM  14253  HG2 MET A1187     141.021 179.561 184.465  1.00  4.25           H
ATOM  14254  HG3 MET A1187     140.747 180.339 183.105  1.00  4.25           H
ATOM  14255  HE1 MET A1187     139.874 177.359 181.304  1.00  4.25           H
ATOM  14256  HE2 MET A1187     139.221 178.150 182.518  1.00  4.25           H
ATOM  14257  HE3 MET A1187     139.829 178.947 181.287  1.00  4.25           H
ATOM  14258  N   MET A1188     144.867 182.685 184.614  1.00  3.50           N
ATOM  14259  CA  MET A1188     146.268 182.963 184.916  1.00  3.50           C
ATOM  14260  C   MET A1188     146.471 183.523 186.321  1.00  3.50           C
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ATOM  14261  O   MET A1188     147.596 183.485 186.830  1.00  3.50        O
ATOM  14262  CB  MET A1188     146.839 183.943 183.891  1.00  3.50        C
ATOM  14263  CG  MET A1188     147.138 183.318 182.539  1.00  3.50        C
ATOM  14264  SD  MET A1188     147.488 184.545 181.266  1.00  3.50        S
ATOM  14265  CE  MET A1188     147.467 183.523 179.795  1.00  3.50        C
ATOM  14266  H   MET A1188     144.531 183.177 183.994  1.00  3.50        H
ATOM  14267  HA  MET A1188     146.769 182.136 184.840  1.00  3.50        H
ATOM  14268  HB2 MET A1188     146.198 184.657 183.751  1.00  3.50        H
ATOM  14269  HB3 MET A1188     147.668 184.309 184.237  1.00  3.50        H
ATOM  14270  HG2 MET A1188     147.913 182.742 182.622  1.00  3.50        H
ATOM  14271  HG3 MET A1188     146.369 182.800 182.254  1.00  3.50        H
ATOM  14272  HE1 MET A1188     147.633 184.083 179.020  1.00  3.50        H
ATOM  14273  HE2 MET A1188     148.159 182.848 179.870  1.00  3.50        H
ATOM  14274  HE3 MET A1188     146.597 183.100 179.717  1.00  3.50        H
ATOM  14275  N   VAL A1189     145.418 184.042 186.958  1.00  4.57        N
ATOM  14276  CA  VAL A1189     145.579 184.694 188.254  1.00  4.57        C
ATOM  14277  C   VAL A1189     145.800 183.691 189.381  1.00  4.57        C
ATOM  14278  O   VAL A1189     146.350 184.054 190.428  1.00  4.57        O
ATOM  14279  CB  VAL A1189     144.354 185.581 188.551  1.00  4.57        C
ATOM  14280  CG1 VAL A1189     144.349 186.032 190.007  1.00  4.57        C
ATOM  14281  CG2 VAL A1189     144.334 186.784 187.620  1.00  4.57        C
ATOM  14282  H   VAL A1189     144.610 184.029 186.664  1.00  4.57        H
ATOM  14283  HA  VAL A1189     146.358 185.270 188.217  1.00  4.57        H
ATOM  14284  HB  VAL A1189     143.547 185.067 188.394  1.00  4.57        H
ATOM  14285 HG11 VAL A1189     143.755 186.793 190.097  1.00  4.57        H
ATOM  14286 HG12 VAL A1189     144.036 185.304 190.567  1.00  4.57        H
ATOM  14287 HG13 VAL A1189     145.249 186.286 190.262  1.00  4.57        H
ATOM  14288 HG21 VAL A1189     143.559 187.329 187.826  1.00  4.57        H
ATOM  14289 HG22 VAL A1189     145.146 187.298 187.751  1.00  4.57        H
ATOM  14290 HG23 VAL A1189     144.284 186.471 186.703  1.00  4.57        H
ATOM  14291  N   GLU A1190     145.395 182.438 189.198  1.00  4.10        N
ATOM  14292  CA  GLU A1190     145.502 181.451 190.265  1.00  4.10        C
ATOM  14293  C   GLU A1190     146.962 181.205 190.629  1.00  4.10        C
ATOM  14294  O   GLU A1190     147.824 181.074 189.755  1.00  4.10        O
ATOM  14295  CB  GLU A1190     144.837 180.144 189.835  1.00  4.10        C
ATOM  14296  CG  GLU A1190     144.684 179.119 190.944  1.00  4.10        C
ATOM  14297  CD  GLU A1190     144.294 177.751 190.418  1.00  4.10        C
ATOM  14298  OE1 GLU A1190     143.296 177.664 189.672  1.00  4.10        O
ATOM  14299  OE2 GLU A1190     144.983 176.764 190.748  1.00  4.10        O
ATOM  14300  H   GLU A1190     145.054 182.135 188.469  1.00  4.10        H
ATOM  14301  HA  GLU A1190     145.044 181.781 191.054  1.00  4.10        H
ATOM  14302  HB2 GLU A1190     143.950 180.345 189.496  1.00  4.10        H
ATOM  14303  HB3 GLU A1190     145.371 179.740 189.133  1.00  4.10        H
ATOM  14304  HG2 GLU A1190     145.525 179.034 191.417  1.00  4.10        H
ATOM  14305  HG3 GLU A1190     143.990 179.415 191.554  1.00  4.10        H
ATOM  14306  N   LYS A1191     147.238 181.140 191.931  1.00  4.84        N
ATOM  14307  CA  LYS A1191     148.595 180.930 192.414  1.00  4.84        C
ATOM  14308  C   LYS A1191     148.553 180.179 193.737  1.00  4.84        C
ATOM  14309  O   LYS A1191     147.526 180.133 194.419  1.00  4.84        O
ATOM  14310  CB  LYS A1191     149.346 182.256 192.585  1.00  4.84        C
ATOM  14311  CG  LYS A1191     148.888 183.078 193.782  1.00  4.84        C
ATOM  14312  CD  LYS A1191     149.101 184.577 193.581  1.00  4.84        C
ATOM  14313  CE  LYS A1191     150.448 184.899 192.941  1.00  4.84        C
ATOM  14314  NZ  LYS A1191     151.585 184.300 193.693  1.00  4.84        N
ATOM  14315  H   LYS A1191     146.652 181.217 192.555  1.00  4.84        H
ATOM  14316  HA  LYS A1191     149.082 180.388 191.774  1.00  4.84        H
ATOM  14317  HB2 LYS A1191     150.291 182.069 192.694  1.00  4.84        H
ATOM  14318  HB3 LYS A1191     149.205 182.789 191.787  1.00  4.84        H
ATOM  14319  HG2 LYS A1191     147.941 182.926 193.928  1.00  4.84        H
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ATOM  14320  HG3 LYS A1191     149.393 182.806 194.564  1.00  4.84           H
ATOM  14321  HD2 LYS A1191     148.403 184.921 193.002  1.00  4.84           H
ATOM  14322  HD3 LYS A1191     149.065 185.020 194.443  1.00  4.84           H
ATOM  14323  HE2 LYS A1191     150.471 184.566 192.031  1.00  4.84           H
ATOM  14324  HE3 LYS A1191     150.569 185.861 192.940  1.00  4.84           H
ATOM  14325  HZ1 LYS A1191     152.352 184.477 193.277  1.00  4.84           H
ATOM  14326  HZ2 LYS A1191     151.618 184.640 194.515  1.00  4.84           H
ATOM  14327  HZ3 LYS A1191     151.484 183.418 193.749  1.00  4.84           H
ATOM  14328  N   GLU A1192     149.692 179.588 194.089  1.00  5.92           N
ATOM  14329  CA  GLU A1192     149.803 178.842 195.335  1.00  5.92           C
ATOM  14330  C   GLU A1192     149.748 179.781 196.533  1.00  5.92           C
ATOM  14331  O   GLU A1192     150.279 180.895 196.497  1.00  5.92           O
ATOM  14332  CB  GLU A1192     151.107 178.044 195.359  1.00  5.92           C
ATOM  14333  CG  GLU A1192     151.145 176.942 196.413  1.00  5.92           C
ATOM  14334  CD  GLU A1192     152.094 177.247 197.560  1.00  5.92           C
ATOM  14335  OE1 GLU A1192     152.441 178.431 197.757  1.00  5.92           O
ATOM  14336  OE2 GLU A1192     152.495 176.299 198.267  1.00  5.92           O
ATOM  14337  H   GLU A1192     150.415 179.605 193.623  1.00  5.92           H
ATOM  14338  HA  GLU A1192     149.062 178.219 195.402  1.00  5.92           H
ATOM  14339  HB2 GLU A1192     151.231 177.628 194.493  1.00  5.92           H
ATOM  14340  HB3 GLU A1192     151.840 178.654 195.531  1.00  5.92           H
ATOM  14341  HG2 GLU A1192     150.256 176.828 196.783  1.00  5.92           H
ATOM  14342  HG3 GLU A1192     151.440 176.119 195.994  1.00  5.92           H
ATOM  14343  N   GLY A1193     149.103 179.321 197.603  1.00  6.35           N
ATOM  14344  CA  GLY A1193     149.020 180.074 198.835  1.00  6.35           C
ATOM  14345  C   GLY A1193     147.904 181.093 198.898  1.00  6.35           C
ATOM  14346  O   GLY A1193     147.751 181.753 199.934  1.00  6.35           O
ATOM  14347  H   GLY A1193     148.699 178.562 197.632  1.00  6.35           H
ATOM  14348  HA2 GLY A1193     148.901 179.456 199.573  1.00  6.35           H
ATOM  14349  HA3 GLY A1193     149.858 180.544 198.972  1.00  6.35           H
ATOM  14350  N   GLN A1194     147.119 181.244 197.836  1.00  6.28           N
ATOM  14351  CA  GLN A1194     146.029 182.207 197.851  1.00  6.28           C
ATOM  14352  C   GLN A1194     144.952 181.780 198.844  1.00  6.28           C
ATOM  14353  O   GLN A1194     144.753 180.591 199.109  1.00  6.28           O
ATOM  14354  CB  GLN A1194     145.431 182.358 196.452  1.00  6.28           C
ATOM  14355  CG  GLN A1194     144.404 181.297 196.090  1.00  6.28           C
ATOM  14356  CD  GLN A1194     144.168 181.201 194.594  1.00  6.28           C
ATOM  14357  OE1 GLN A1194     144.854 181.845 193.801  1.00  6.28           O
ATOM  14358  NE2 GLN A1194     143.191 180.392 194.202  1.00  6.28           N
ATOM  14359  H   GLN A1194     147.198 180.806 197.100  1.00  6.28           H
ATOM  14360  HA  GLN A1194     146.369 183.071 198.131  1.00  6.28           H
ATOM  14361  HB2 GLN A1194     144.994 183.222 196.393  1.00  6.28           H
ATOM  14362  HB3 GLN A1194     146.149 182.310 195.803  1.00  6.28           H
ATOM  14363  HG2 GLN A1194     144.717 180.433 196.401  1.00  6.28           H
ATOM  14364  HG3 GLN A1194     143.558 181.516 196.511  1.00  6.28           H
ATOM  14365 HE21 GLN A1194     142.732 179.958 194.786  1.00  6.28           H
ATOM  14366 HE22 GLN A1194     143.017 180.302 193.365  1.00  6.28           H
ATOM  14367  N   SER A1195     144.259 182.769 199.399  1.00  9.34           N
ATOM  14368  CA  SER A1195     143.211 182.496 200.369  1.00  9.34           C
ATOM  14369  C   SER A1195     142.035 181.789 199.704  1.00  9.34           C
ATOM  14370  O   SER A1195     141.815 181.899 198.495  1.00  9.34           O
ATOM  14371  CB  SER A1195     142.738 183.795 201.022  1.00  9.34           C
ATOM  14372  OG  SER A1195     141.955 184.562 200.124  1.00  9.34           O
ATOM  14373  H   SER A1195     144.377 183.604 199.228  1.00  9.34           H
ATOM  14374  HA  SER A1195     143.561 181.916 201.063  1.00  9.34           H
ATOM  14375  HB2 SER A1195     142.204 183.581 201.802  1.00  9.34           H
ATOM  14376  HB3 SER A1195     143.515 184.313 201.284  1.00  9.34           H
ATOM  14377  HG  SER A1195     141.720 185.281 200.490  1.00  9.34           H
ATOM  14378  N   GLN A1196     141.280 181.042 200.513  1.00 11.80           N
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ATOM  14379  CA  GLN A1196     140.120 180.324 199.991  1.00 11.80           C
ATOM  14380  C   GLN A1196     139.088 181.277 199.395  1.00 11.80           C
ATOM  14381  O   GLN A1196     138.363 180.905 198.463  1.00 11.80           O
ATOM  14382  CB  GLN A1196     139.483 179.459 201.088  1.00 11.80           C
ATOM  14383  CG  GLN A1196     138.835 180.195 202.274  1.00 11.80           C
ATOM  14384  CD  GLN A1196     139.674 181.324 202.837  1.00 11.80           C
ATOM  14385  OE1 GLN A1196     140.795 181.109 203.298  1.00 11.80           O
ATOM  14386  NE2 GLN A1196     139.136 182.536 202.802  1.00 11.80           N
ATOM  14387  H   GLN A1196     141.433 180.926 201.350  1.00 11.80           H
ATOM  14388  HA  GLN A1196     140.416 179.731 199.283  1.00 11.80           H
ATOM  14389  HB2 GLN A1196     138.796 178.910 200.682  1.00 11.80           H
ATOM  14390  HB3 GLN A1196     140.175 178.886 201.455  1.00 11.80           H
ATOM  14391  HG2 GLN A1196     137.988 180.568 201.987  1.00 11.80           H
ATOM  14392  HG3 GLN A1196     138.686 179.556 202.989  1.00 11.80           H
ATOM  14393 HE21 GLN A1196     138.351 182.646 202.468  1.00 11.80           H
ATOM  14394 HE22 GLN A1196     139.573 183.211 203.106  1.00 11.80           H
ATOM  14395  N   HIS A1197     139.010 182.508 199.909  1.00  8.61           N
ATOM  14396  CA  HIS A1197     138.066 183.481 199.365  1.00  8.61           C
ATOM  14397  C   HIS A1197     138.387 183.793 197.908  1.00  8.61           C
ATOM  14398  O   HIS A1197     137.484 183.874 197.064  1.00  8.61           O
ATOM  14399  CB  HIS A1197     138.094 184.753 200.216  1.00  8.61           C
ATOM  14400  CG  HIS A1197     137.290 185.884 199.652  1.00  8.61           C
ATOM  14401  ND1 HIS A1197     135.918 185.835 199.528  1.00  8.61           N
ATOM  14402  CD2 HIS A1197     137.666 187.098 199.185  1.00  8.61           C
ATOM  14403  CE1 HIS A1197     135.484 186.970 199.009  1.00  8.61           C
ATOM  14404  NE2 HIS A1197     136.525 187.753 198.791  1.00  8.61           N
ATOM  14405  H   HIS A1197     139.492 182.803 200.555  1.00  8.61           H
ATOM  14406  HA  HIS A1197     137.171 183.112 199.404  1.00  8.61           H
ATOM  14407  HB2 HIS A1197     137.738 184.549 201.095  1.00  8.61           H
ATOM  14408  HB3 HIS A1197     139.012 185.053 200.298  1.00  8.61           H
ATOM  14409  HD1 HIS A1197     135.422 185.171 199.755  1.00  8.61           H
ATOM  14410  HD2 HIS A1197     138.535 187.426 199.139  1.00  8.61           H
ATOM  14411  HE1 HIS A1197     134.597 187.181 198.826  1.00  8.61           H
ATOM  14412  N   MET A1198     139.674 183.962 197.594  1.00 11.33           N
ATOM  14413  CA  MET A1198     140.077 184.199 196.212  1.00 11.33           C
ATOM  14414  C   MET A1198     139.711 183.012 195.331  1.00 11.33           C
ATOM  14415  O   MET A1198     139.263 183.185 194.191  1.00 11.33           O
ATOM  14416  CB  MET A1198     141.581 184.474 196.147  1.00 11.33           C
ATOM  14417  CG  MET A1198     142.089 184.862 194.766  1.00 11.33           C
ATOM  14418  SD  MET A1198     141.586 186.524 194.280  1.00 11.33           S
ATOM  14419  CE  MET A1198     142.860 186.930 193.089  1.00 11.33           C
ATOM  14420  H   MET A1198     140.324 183.938 198.158  1.00 11.33           H
ATOM  14421  HA  MET A1198     139.617 184.987 195.883  1.00 11.33           H
ATOM  14422  HB2 MET A1198     141.793 185.199 196.756  1.00 11.33           H
ATOM  14423  HB3 MET A1198     142.053 183.671 196.418  1.00 11.33           H
ATOM  14424  HG2 MET A1198     143.059 184.835 194.770  1.00 11.33           H
ATOM  14425  HG3 MET A1198     141.744 184.239 194.109  1.00 11.33           H
ATOM  14426  HE1 MET A1198     142.692 187.820 192.740  1.00 11.33           H
ATOM  14427  HE2 MET A1198     143.724 186.904 193.528  1.00 11.33           H
ATOM  14428  HE3 MET A1198     142.834 186.282 192.368  1.00 11.33           H
ATOM  14429  N   THR A1199     139.902 181.795 195.844  1.00  7.76           N
ATOM  14430  CA  THR A1199     139.513 180.603 195.099  1.00  7.76           C
ATOM  14431  C   THR A1199     138.023 180.627 194.782  1.00  7.76           C
ATOM  14432  O   THR A1199     137.607 180.318 193.658  1.00  7.76           O
ATOM  14433  CB  THR A1199     139.872 179.348 195.898  1.00  7.76           C
ATOM  14434  OG1 THR A1199     141.270 179.362 196.215  1.00  7.76           O
ATOM  14435  CG2 THR A1199     139.548 178.088 195.105  1.00  7.76           C
ATOM  14436  H   THR A1199     140.253 181.636 196.614  1.00  7.76           H
ATOM  14437  HA  THR A1199     139.999 180.579 194.260  1.00  7.76           H
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ATOM  14438  HB  THR A1199     139.357 179.333 196.720  1.00  7.76           H
ATOM  14439  HG1 THR A1199     141.465 178.690 196.680  1.00  7.76           H
ATOM  14440 HG21 THR A1199     139.885 177.309 195.574  1.00  7.76           H
ATOM  14441 HG22 THR A1199     138.589 177.998 194.997  1.00  7.76           H
ATOM  14442 HG23 THR A1199     139.963 178.131 194.230  1.00  7.76           H
ATOM  14443  N   GLU A1200     137.201 180.995 195.768  1.00  9.58           N
ATOM  14444  CA  GLU A1200     135.760 181.051 195.537  1.00  9.58           C
ATOM  14445  C   GLU A1200     135.408 182.096 194.486  1.00  9.58           C
ATOM  14446  O   GLU A1200     134.570 181.848 193.610  1.00  9.58           O
ATOM  14447  CB  GLU A1200     135.028 181.339 196.848  1.00  9.58           C
ATOM  14448  CG  GLU A1200     135.188 180.251 197.895  1.00  9.58           C
ATOM  14449  CD  GLU A1200     134.883 178.869 197.350  1.00  9.58           C
ATOM  14450  OE1 GLU A1200     133.709 178.610 197.012  1.00  9.58           O
ATOM  14451  OE2 GLU A1200     135.818 178.047 197.250  1.00  9.58           O
ATOM  14452  H   GLU A1200     137.448 181.214 196.563  1.00  9.58           H
ATOM  14453  HA  GLU A1200     135.463 180.193 195.198  1.00  9.58           H
ATOM  14454  HB2 GLU A1200     135.371 182.165 197.225  1.00  9.58           H
ATOM  14455  HB3 GLU A1200     134.080 181.436 196.662  1.00  9.58           H
ATOM  14456  HG2 GLU A1200     136.104 180.249 198.213  1.00  9.58           H
ATOM  14457  HG3 GLU A1200     134.582 180.428 198.631  1.00  9.58           H
ATOM  14458  N   VAL A1201     136.035 183.273 194.554  1.00  6.93           N
ATOM  14459  CA  VAL A1201     135.735 184.312 193.568  1.00  6.93           C
ATOM  14460  C   VAL A1201     136.112 183.837 192.170  1.00  6.93           C
ATOM  14461  O   VAL A1201     135.361 184.035 191.205  1.00  6.93           O
ATOM  14462  CB  VAL A1201     136.440 185.639 193.912  1.00  6.93           C
ATOM  14463  CG1 VAL A1201     135.731 186.802 193.236  1.00  6.93           C
ATOM  14464  CG2 VAL A1201     136.485 185.877 195.410  1.00  6.93           C
ATOM  14465  H   VAL A1201     136.627 183.479 195.142  1.00  6.93           H
ATOM  14466  HA  VAL A1201     134.779 184.478 193.574  1.00  6.93           H
ATOM  14467  HB  VAL A1201     137.352 185.608 193.583  1.00  6.93           H
ATOM  14468 HG11 VAL A1201     136.205 187.623 193.440  1.00  6.93           H
ATOM  14469 HG12 VAL A1201     135.729 186.650 192.278  1.00  6.93           H
ATOM  14470 HG13 VAL A1201     134.819 186.856 193.566  1.00  6.93           H
ATOM  14471 HG21 VAL A1201     136.220 186.791 195.595  1.00  6.93           H
ATOM  14472 HG22 VAL A1201     135.880 185.270 195.862  1.00  6.93           H
ATOM  14473 HG23 VAL A1201     137.393 185.732 195.715  1.00  6.93           H
ATOM  14474  N   LEU A1202     137.285 183.214 192.035  1.00  6.12           N
ATOM  14475  CA  LEU A1202     137.714 182.735 190.725  1.00  6.12           C
ATOM  14476  C   LEU A1202     136.765 181.668 190.192  1.00  6.12           C
ATOM  14477  O   LEU A1202     136.412 181.675 189.006  1.00  6.12           O
ATOM  14478  CB  LEU A1202     139.142 182.195 190.810  1.00  6.12           C
ATOM  14479  CG  LEU A1202     140.233 183.225 191.122  1.00  6.12           C
ATOM  14480  CD1 LEU A1202     141.603 182.562 191.169  1.00  6.12           C
ATOM  14481  CD2 LEU A1202     140.224 184.365 190.113  1.00  6.12           C
ATOM  14482  H   LEU A1202     137.840 183.061 192.675  1.00  6.12           H
ATOM  14483  HA  LEU A1202     137.705 183.476 190.099  1.00  6.12           H
ATOM  14484  HB2 LEU A1202     139.172 181.523 191.509  1.00  6.12           H
ATOM  14485  HB3 LEU A1202     139.365 181.786 189.959  1.00  6.12           H
ATOM  14486  HG  LEU A1202     140.062 183.607 191.996  1.00  6.12           H
ATOM  14487 HD11 LEU A1202     142.273 183.235 191.366  1.00  6.12           H
ATOM  14488 HD12 LEU A1202     141.601 181.883 191.862  1.00  6.12           H
ATOM  14489 HD13 LEU A1202     141.787 182.155 190.308  1.00  6.12           H
ATOM  14490 HD21 LEU A1202     141.026 184.897 190.231  1.00  6.12           H
ATOM  14491 HD22 LEU A1202     140.201 183.994 189.218  1.00  6.12           H
ATOM  14492 HD23 LEU A1202     139.439 184.914 190.264  1.00  6.12           H
ATOM  14493  N   TYR A1203     136.337 180.743 191.055  1.00  6.87           N
ATOM  14494  CA  TYR A1203     135.408 179.707 190.614  1.00  6.87           C
ATOM  14495  C   TYR A1203     134.077 180.310 190.178  1.00  6.87           C
ATOM  14496  O   TYR A1203     133.490 179.879 189.179  1.00  6.87           O
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ATOM  14497  CB  TYR A1203     135.199 178.680 191.729  1.00  6.87           C
ATOM  14498  CG  TYR A1203     136.368 177.734 191.955  1.00  6.87           C
ATOM  14499  CD1 TYR A1203     137.437 177.678 191.066  1.00  6.87           C
ATOM  14500  CD2 TYR A1203     136.396 176.891 193.059  1.00  6.87           C
ATOM  14501  CE1 TYR A1203     138.497 176.816 191.273  1.00  6.87           C
ATOM  14502  CE2 TYR A1203     137.453 176.025 193.274  1.00  6.87           C
ATOM  14503  CZ  TYR A1203     138.499 175.991 192.378  1.00  6.87           C
ATOM  14504  OH  TYR A1203     139.554 175.132 192.586  1.00  6.87           O
ATOM  14505  H   TYR A1203     136.566 180.694 191.882  1.00  6.87           H
ATOM  14506  HA  TYR A1203     135.776 179.256 189.838  1.00  6.87           H
ATOM  14507  HB2 TYR A1203     135.041 179.154 192.561  1.00  6.87           H
ATOM  14508  HB3 TYR A1203     134.423 178.140 191.511  1.00  6.87           H
ATOM  14509  HD1 TYR A1203     137.444 178.230 190.319  1.00  6.87           H
ATOM  14510  HD2 TYR A1203     135.692 176.910 193.666  1.00  6.87           H
ATOM  14511  HE1 TYR A1203     139.204 176.791 190.670  1.00  6.87           H
ATOM  14512  HE2 TYR A1203     137.457 175.467 194.018  1.00  6.87           H
ATOM  14513  HH  TYR A1203     139.436 174.698 193.295  1.00  6.87           H
ATOM  14514  N   TRP A1204     133.582 181.308 190.914  1.00  6.27           N
ATOM  14515  CA  TRP A1204     132.326 181.944 190.525  1.00  6.27           C
ATOM  14516  C   TRP A1204     132.465 182.673 189.191  1.00  6.27           C
ATOM  14517  O   TRP A1204     131.551 182.638 188.357  1.00  6.27           O
ATOM  14518  CB  TRP A1204     131.860 182.901 191.621  1.00  6.27           C
ATOM  14519  CG  TRP A1204     131.146 182.205 192.743  1.00  6.27           C
ATOM  14520  CD1 TRP A1204     131.610 182.003 194.011  1.00  6.27           C
ATOM  14521  CD2 TRP A1204     129.845 181.607 192.693  1.00  6.27           C
ATOM  14522  NE1 TRP A1204     130.677 181.322 194.754  1.00  6.27           N
ATOM  14523  CE2 TRP A1204     129.585 181.066 193.968  1.00  6.27           C
ATOM  14524  CE3 TRP A1204     128.875 181.478 191.695  1.00  6.27           C
ATOM  14525  CZ2 TRP A1204     128.394 180.408 194.271  1.00  6.27           C
ATOM  14526  CZ3 TRP A1204     127.693 180.825 191.998  1.00  6.27           C
ATOM  14527  CH2 TRP A1204     127.464 180.298 193.275  1.00  6.27           C
ATOM  14528  H   TRP A1204     133.944 181.627 191.626  1.00  6.27           H
ATOM  14529  HA  TRP A1204     131.647 181.259 190.420  1.00  6.27           H
ATOM  14530  HB2 TRP A1204     132.632 183.354 191.994  1.00  6.27           H
ATOM  14531  HB3 TRP A1204     131.250 183.549 191.236  1.00  6.27           H
ATOM  14532  HD1 TRP A1204     132.437 182.287 194.327  1.00  6.27           H
ATOM  14533  HE1 TRP A1204     130.765 181.092 195.578  1.00  6.27           H
ATOM  14534  HE3 TRP A1204     129.020 181.826 190.845  1.00  6.27           H
ATOM  14535  HZ2 TRP A1204     128.239 180.057 195.118  1.00  6.27           H
ATOM  14536  HZ3 TRP A1204     127.041 180.733 191.342  1.00  6.27           H
ATOM  14537  HH2 TRP A1204     126.660 179.863 193.450  1.00  6.27           H
ATOM  14538  N   ILE A1205     133.601 183.337 188.968  1.00  5.39           N
ATOM  14539  CA  ILE A1205     133.829 183.991 187.681  1.00  5.39           C
ATOM  14540  C   ILE A1205     133.842 182.958 186.560  1.00  5.39           C
ATOM  14541  O   ILE A1205     133.293 183.185 185.470  1.00  5.39           O
ATOM  14542  CB  ILE A1205     135.137 184.803 187.722  1.00  5.39           C
ATOM  14543  CG1 ILE A1205     134.982 186.009 188.652  1.00  5.39           C
ATOM  14544  CG2 ILE A1205     135.527 185.253 186.319  1.00  5.39           C
ATOM  14545  CD1 ILE A1205     136.292 186.688 189.004  1.00  5.39           C
ATOM  14546  H   ILE A1205     134.242 183.422 189.535  1.00  5.39           H
ATOM  14547  HA  ILE A1205     133.101 184.608 187.509  1.00  5.39           H
ATOM  14548  HB  ILE A1205     135.842 184.233 188.070  1.00  5.39           H
ATOM  14549 HG12 ILE A1205     134.415 186.666 188.219  1.00  5.39           H
ATOM  14550 HG13 ILE A1205     134.571 185.715 189.480  1.00  5.39           H
ATOM  14551 HG21 ILE A1205     136.186 185.961 186.385  1.00  5.39           H
ATOM  14552 HG22 ILE A1205     135.903 184.501 185.836  1.00  5.39           H
ATOM  14553 HG23 ILE A1205     134.737 185.581 185.863  1.00  5.39           H
ATOM  14554 HD11 ILE A1205     136.137 187.314 189.729  1.00  5.39           H
ATOM  14555 HD12 ILE A1205     136.932 186.014 189.281  1.00  5.39           H
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ATOM  14556 HD13 ILE A1205     136.625 187.161 188.225  1.00  5.39           H
ATOM  14557  N   ASN A1206     134.473 181.808 186.806  1.00  5.12           N
ATOM  14558  CA  ASN A1206     134.484 180.747 185.804  1.00  5.12           C
ATOM  14559  C   ASN A1206     133.073 180.245 185.518  1.00  5.12           C
ATOM  14560  O   ASN A1206     132.730 179.955 184.365  1.00  5.12           O
ATOM  14561  CB  ASN A1206     135.381 179.600 186.267  1.00  5.12           C
ATOM  14562  CG  ASN A1206     136.850 179.872 186.013  1.00  5.12           C
ATOM  14563  OD1 ASN A1206     137.432 179.358 185.058  1.00  5.12           O
ATOM  14564  ND2 ASN A1206     137.459 180.686 186.867  1.00  5.12           N
ATOM  14565  H   ASN A1206     134.895 181.622 187.532  1.00  5.12           H
ATOM  14566  HA  ASN A1206     134.850 181.098 184.977  1.00  5.12           H
ATOM  14567  HB2 ASN A1206     135.260 179.469 187.221  1.00  5.12           H
ATOM  14568  HB3 ASN A1206     135.137 178.793 185.787  1.00  5.12           H
ATOM  14569 HD21 ASN A1206     138.292 180.871 186.765  1.00  5.12           H
ATOM  14570 HD22 ASN A1206     137.019 181.027 187.523  1.00  5.12           H
ATOM  14571  N   VAL A1207     132.242 180.123 186.556  1.00  6.12           N
ATOM  14572  CA  VAL A1207     130.858 179.699 186.340  1.00  6.12           C
ATOM  14573  C   VAL A1207     130.117 180.730 185.497  1.00  6.12           C
ATOM  14574  O   VAL A1207     129.292 180.382 184.642  1.00  6.12           O
ATOM  14575  CB  VAL A1207     130.132 179.446 187.682  1.00  6.12           C
ATOM  14576  CG1 VAL A1207     130.775 178.418 188.645  1.00  6.12           C
ATOM  14577  CG2 VAL A1207     129.141 180.535 188.171  1.00  6.12           C
ATOM  14578  H   VAL A1207     132.465 180.275 187.372  1.00  6.12           H
ATOM  14579  HA  VAL A1207     130.862 178.864 185.846  1.00  6.12           H
ATOM  14580  HB  VAL A1207     130.777 180.045 188.082  1.00  6.12           H
ATOM  14581 HG11 VAL A1207     130.530 178.644 189.556  1.00  6.12           H
ATOM  14582 HG12 VAL A1207     130.447 177.532 188.424  1.00  6.12           H
ATOM  14583 HG13 VAL A1207     131.737 178.449 188.544  1.00  6.12           H
ATOM  14584 HG21 VAL A1207     128.878 180.334 189.082  1.00  6.12           H
ATOM  14585 HG22 VAL A1207     129.574 181.401 188.136  1.00  6.12           H
ATOM  14586 HG23 VAL A1207     128.361 180.533 187.594  1.00  6.12           H
ATOM  14587  N   VAL A1208     130.388 182.015 185.732  1.00  5.50           N
ATOM  14588  CA  VAL A1208     129.768 183.063 184.922  1.00  5.50           C
ATOM  14589  C   VAL A1208     130.164 182.900 183.458  1.00  5.50           C
ATOM  14590  O   VAL A1208     129.328 183.002 182.549  1.00  5.50           O
ATOM  14591  CB  VAL A1208     130.154 184.454 185.459  1.00  5.50           C
ATOM  14592  CG1 VAL A1208     129.787 185.537 184.452  1.00  5.50           C
ATOM  14593  CG2 VAL A1208     129.480 184.713 186.797  1.00  5.50           C
ATOM  14594  H   VAL A1208     130.919 182.302 186.345  1.00  5.50           H
ATOM  14595  HA  VAL A1208     128.803 182.978 184.982  1.00  5.50           H
ATOM  14596  HB  VAL A1208     131.113 184.485 185.595  1.00  5.50           H
ATOM  14597 HG11 VAL A1208     129.767 186.394 184.907  1.00  5.50           H
ATOM  14598 HG12 VAL A1208     130.451 185.556 183.746  1.00  5.50           H
ATOM  14599 HG13 VAL A1208     128.912 185.342 184.082  1.00  5.50           H
ATOM  14600 HG21 VAL A1208     129.769 185.576 187.134  1.00  5.50           H
ATOM  14601 HG22 VAL A1208     128.518 184.711 186.672  1.00  5.50           H
ATOM  14602 HG23 VAL A1208     129.734 184.014 187.419  1.00  5.50           H
ATOM  14603  N   PHE A1209     131.451 182.650 183.211  1.00  5.46           N
ATOM  14604  CA  PHE A1209     131.908 182.439 181.838  1.00  5.46           C
ATOM  14605  C   PHE A1209     131.227 181.226 181.211  1.00  5.46           C
ATOM  14606  O   PHE A1209     130.847 181.251 180.032  1.00  5.46           O
ATOM  14607  CB  PHE A1209     133.427 182.267 181.811  1.00  5.46           C
ATOM  14608  CG  PHE A1209     134.184 183.562 181.722  1.00  5.46           C
ATOM  14609  CD1 PHE A1209     134.120 184.343 180.579  1.00  5.46           C
ATOM  14610  CD2 PHE A1209     134.965 183.997 182.780  1.00  5.46           C
ATOM  14611  CE1 PHE A1209     134.817 185.533 180.495  1.00  5.46           C
ATOM  14612  CE2 PHE A1209     135.664 185.187 182.701  1.00  5.46           C
ATOM  14613  CZ  PHE A1209     135.590 185.955 181.558  1.00  5.46           C
ATOM  14614  H   PHE A1209     132.068 182.599 183.808  1.00  5.46           H
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ATOM  14615  HA  PHE A1209     131.682 183.217 181.307  1.00  5.46           H
ATOM  14616  HB2 PHE A1209     133.706 181.817 182.624  1.00  5.46           H
ATOM  14617  HB3 PHE A1209     133.667 181.731 181.040  1.00  5.46           H
ATOM  14618  HD1 PHE A1209     133.600 184.063 179.860  1.00  5.46           H
ATOM  14619  HD2 PHE A1209     135.018 183.483 183.553  1.00  5.46           H
ATOM  14620  HE1 PHE A1209     134.766 186.049 179.723  1.00  5.46           H
ATOM  14621  HE2 PHE A1209     136.184 185.469 183.419  1.00  5.46           H
ATOM  14622  HZ  PHE A1209     136.060 186.756 181.503  1.00  5.46           H
ATOM  14623  N   ILE A1210     131.080 180.147 181.983  1.00  6.24           N
ATOM  14624  CA  ILE A1210     130.420 178.949 181.473  1.00  6.24           C
ATOM  14625  C   ILE A1210     128.979 179.262 181.094  1.00  6.24           C
ATOM  14626  O   ILE A1210     128.478 178.807 180.059  1.00  6.24           O
ATOM  14627  CB  ILE A1210     130.498 177.814 182.513  1.00  6.24           C
ATOM  14628  CG1 ILE A1210     131.882 177.163 182.483  1.00  6.24           C
ATOM  14629  CG2 ILE A1210     129.419 176.769 182.253  1.00  6.24           C
ATOM  14630  CD1 ILE A1210     132.196 176.339 183.712  1.00  6.24           C
ATOM  14631  H   ILE A1210     131.352 180.086 182.797  1.00  6.24           H
ATOM  14632  HA  ILE A1210     130.881 178.652 180.673  1.00  6.24           H
ATOM  14633  HB  ILE A1210     130.354 178.193 183.394  1.00  6.24           H
ATOM  14634 HG12 ILE A1210     131.935 176.578 181.711  1.00  6.24           H
ATOM  14635 HG13 ILE A1210     132.553 177.860 182.414  1.00  6.24           H
ATOM  14636 HG21 ILE A1210     129.649 175.956 182.729  1.00  6.24           H
ATOM  14637 HG22 ILE A1210     128.566 177.103 182.572  1.00  6.24           H
ATOM  14638 HG23 ILE A1210     129.374 176.589 181.301  1.00  6.24           H
ATOM  14639 HD11 ILE A1210     133.154 176.193 183.759  1.00  6.24           H
ATOM  14640 HD12 ILE A1210     131.895 176.819 184.499  1.00  6.24           H
ATOM  14641 HD13 ILE A1210     131.734 175.488 183.648  1.00  6.24           H
ATOM  14642  N   ILE A1211     128.286 180.033 181.935  1.00  6.76           N
ATOM  14643  CA  ILE A1211     126.910 180.415 181.631  1.00  6.76           C
ATOM  14644  C   ILE A1211     126.859 181.225 180.342  1.00  6.76           C
ATOM  14645  O   ILE A1211     125.964 181.038 179.507  1.00  6.76           O
ATOM  14646  CB  ILE A1211     126.298 181.194 182.810  1.00  6.76           C
ATOM  14647  CG1 ILE A1211     126.085 180.263 184.006  1.00  6.76           C
ATOM  14648  CG2 ILE A1211     124.984 181.846 182.391  1.00  6.76           C
ATOM  14649  CD1 ILE A1211     125.759 180.986 185.296  1.00  6.76           C
ATOM  14650  H   ILE A1211     128.587 180.343 182.678  1.00  6.76           H
ATOM  14651  HA  ILE A1211     126.382 179.612 181.499  1.00  6.76           H
ATOM  14652  HB  ILE A1211     126.918 181.893 183.071  1.00  6.76           H
ATOM  14653 HG12 ILE A1211     125.348 179.665 183.807  1.00  6.76           H
ATOM  14654 HG13 ILE A1211     126.895 179.750 184.151  1.00  6.76           H
ATOM  14655 HG21 ILE A1211     124.486 182.098 183.183  1.00  6.76           H
ATOM  14656 HG22 ILE A1211     125.174 182.635 181.860  1.00  6.76           H
ATOM  14657 HG23 ILE A1211     124.470 181.210 181.869  1.00  6.76           H
ATOM  14658 HD11 ILE A1211     125.836 180.363 186.035  1.00  6.76           H
ATOM  14659 HD12 ILE A1211     126.385 181.718 185.414  1.00  6.76           H
ATOM  14660 HD13 ILE A1211     124.854 181.331 185.247  1.00  6.76           H
ATOM  14661  N   LEU A1212     127.807 182.148 180.167  1.00  5.76           N
ATOM  14662  CA  LEU A1212     127.823 182.959 178.952  1.00  5.76           C
ATOM  14663  C   LEU A1212     128.017 182.092 177.711  1.00  5.76           C
ATOM  14664  O   LEU A1212     127.337 182.283 176.693  1.00  5.76           O
ATOM  14665  CB  LEU A1212     128.923 184.016 179.044  1.00  5.76           C
ATOM  14666  CG  LEU A1212     128.609 185.236 179.913  1.00  5.76           C
ATOM  14667  CD1 LEU A1212     129.853 186.091 180.097  1.00  5.76           C
ATOM  14668  CD2 LEU A1212     127.478 186.057 179.310  1.00  5.76           C
ATOM  14669  H   LEU A1212     128.439 182.320 180.724  1.00  5.76           H
ATOM  14670  HA  LEU A1212     126.971 183.413 178.866  1.00  5.76           H
ATOM  14671  HB2 LEU A1212     129.718 183.598 179.409  1.00  5.76           H
ATOM  14672  HB3 LEU A1212     129.111 184.339 178.149  1.00  5.76           H
ATOM  14673  HG  LEU A1212     128.323 184.933 180.789  1.00  5.76           H
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ATOM  14674 HD11 LEU A1212     129.645 186.826 180.695  1.00  5.76           H
ATOM  14675 HD12 LEU A1212     130.558 185.544 180.478  1.00  5.76           H
ATOM  14676 HD13 LEU A1212     130.131 186.434 179.234  1.00  5.76           H
ATOM  14677 HD21 LEU A1212     127.417 186.903 179.781  1.00  5.76           H
ATOM  14678 HD22 LEU A1212     127.667 186.213 178.372  1.00  5.76           H
ATOM  14679 HD23 LEU A1212     126.646 185.567 179.403  1.00  5.76           H
ATOM  14680  N   PHE A1213     128.945 181.136 177.774  1.00  6.22           N
ATOM  14681  CA  PHE A1213     129.167 180.257 176.627  1.00  6.22           C
ATOM  14682  C   PHE A1213     127.944 179.387 176.353  1.00  6.22           C
ATOM  14683  O   PHE A1213     127.591 179.146 175.190  1.00  6.22           O
ATOM  14684  CB  PHE A1213     130.410 179.397 176.859  1.00  6.22           C
ATOM  14685  CG  PHE A1213     131.690 180.187 176.923  1.00  6.22           C
ATOM  14686  CD1 PHE A1213     131.949 181.191 176.003  1.00  6.22           C
ATOM  14687  CD2 PHE A1213     132.631 179.930 177.906  1.00  6.22           C
ATOM  14688  CE1 PHE A1213     133.122 181.919 176.060  1.00  6.22           C
ATOM  14689  CE2 PHE A1213     133.806 180.656 177.968  1.00  6.22           C
ATOM  14690  CZ  PHE A1213     134.052 181.651 177.044  1.00  6.22           C
ATOM  14691  H   PHE A1213     129.449 180.978 178.453  1.00  6.22           H
ATOM  14692  HA  PHE A1213     129.316 180.802 175.839  1.00  6.22           H
ATOM  14693  HB2 PHE A1213     130.311 178.925 177.700  1.00  6.22           H
ATOM  14694  HB3 PHE A1213     130.490 178.761 176.132  1.00  6.22           H
ATOM  14695  HD1 PHE A1213     131.327 181.376 175.337  1.00  6.22           H
ATOM  14696  HD2 PHE A1213     132.470 179.260 178.531  1.00  6.22           H
ATOM  14697  HE1 PHE A1213     133.285 182.589 175.436  1.00  6.22           H
ATOM  14698  HE2 PHE A1213     134.431 180.474 178.632  1.00  6.22           H
ATOM  14699  HZ  PHE A1213     134.842 182.140 177.085  1.00  6.22           H
ATOM  14700  N   THR A1214     127.284 178.906 177.409  1.00  8.09           N
ATOM  14701  CA  THR A1214     126.057 178.139 177.222  1.00  8.09           C
ATOM  14702  C   THR A1214     124.989 178.981 176.535  1.00  8.09           C
ATOM  14703  O   THR A1214     124.275 178.494 175.650  1.00  8.09           O
ATOM  14704  CB  THR A1214     125.545 177.628 178.569  1.00  8.09           C
ATOM  14705  OG1 THR A1214     126.548 176.814 179.190  1.00  8.09           O
ATOM  14706  CG2 THR A1214     124.273 176.809 178.386  1.00  8.09           C
ATOM  14707  H   THR A1214     127.522 179.009 178.229  1.00  8.09           H
ATOM  14708  HA  THR A1214     126.244 177.372 176.659  1.00  8.09           H
ATOM  14709  HB  THR A1214     125.342 178.383 179.143  1.00  8.09           H
ATOM  14710  HG1 THR A1214     126.270 176.529 179.929  1.00  8.09           H
ATOM  14711 HG21 THR A1214     124.071 176.327 179.203  1.00  8.09           H
ATOM  14712 HG22 THR A1214     123.527 177.391 178.173  1.00  8.09           H
ATOM  14713 HG23 THR A1214     124.391 176.170 177.666  1.00  8.09           H
ATOM  14714  N   GLY A1215     124.859 180.245 176.938  1.00  9.16           N
ATOM  14715  CA  GLY A1215     123.908 181.126 176.281  1.00  9.16           C
ATOM  14716  C   GLY A1215     124.238 181.343 174.817  1.00  9.16           C
ATOM  14717  O   GLY A1215     123.344 181.378 173.966  1.00  9.16           O
ATOM  14718  H   GLY A1215     125.303 180.608 177.579  1.00  9.16           H
ATOM  14719  HA2 GLY A1215     123.018 180.744 176.342  1.00  9.16           H
ATOM  14720  HA3 GLY A1215     123.904 181.987 176.726  1.00  9.16           H
ATOM  14721  N   GLU A1216     125.526 181.502 174.505  1.00 10.96           N
ATOM  14722  CA  GLU A1216     125.936 181.624 173.108  1.00 10.96           C
ATOM  14723  C   GLU A1216     125.514 180.391 172.316  1.00 10.96           C
ATOM  14724  O   GLU A1216     124.975 180.498 171.205  1.00 10.96           O
ATOM  14725  CB  GLU A1216     127.451 181.829 173.028  1.00 10.96           C
ATOM  14726  CG  GLU A1216     128.046 181.767 171.613  1.00 10.96           C
ATOM  14727  CD  GLU A1216     129.404 181.084 171.561  1.00 10.96           C
ATOM  14728  OE1 GLU A1216     129.829 180.496 172.578  1.00 10.96           O
ATOM  14729  OE2 GLU A1216     130.047 181.132 170.491  1.00 10.96           O
ATOM  14730  H   GLU A1216     126.170 181.542 175.073  1.00 10.96           H
ATOM  14731  HA  GLU A1216     125.504 182.399 172.715  1.00 10.96           H
ATOM  14732  HB2 GLU A1216     127.663 182.702 173.394  1.00 10.96           H
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ATOM  14733  HB3 GLU A1216     127.875 181.143 173.564  1.00 10.96           H
ATOM  14734  HG2 GLU A1216     127.454 181.290 171.014  1.00 10.96           H
ATOM  14735  HG3 GLU A1216     128.167 182.674 171.294  1.00 10.96           H
ATOM  14736  N   CYS A1217     125.760 179.205 172.877  1.00 12.05           N
ATOM  14737  CA  CYS A1217     125.382 177.973 172.191  1.00 12.05           C
ATOM  14738  C   CYS A1217     123.875 177.901 171.979  1.00 12.05           C
ATOM  14739  O   CYS A1217     123.409 177.501 170.905  1.00 12.05           O
ATOM  14740  CB  CYS A1217     125.868 176.760 172.984  1.00 12.05           C
ATOM  14741  SG  CYS A1217     125.818 175.203 172.065  1.00 12.05           S
ATOM  14742  H   CYS A1217     126.137 179.089 173.641  1.00 12.05           H
ATOM  14743  HA  CYS A1217     125.809 177.953 171.320  1.00 12.05           H
ATOM  14744  HB2 CYS A1217     126.787 176.914 173.255  1.00 12.05           H
ATOM  14745  HB3 CYS A1217     125.308 176.658 173.769  1.00 12.05           H
ATOM  14746  HG  CYS A1217     126.206 174.317 172.774  1.00 12.05           H
ATOM  14747  N   VAL A1218     123.096 178.276 172.996  1.00 13.11           N
ATOM  14748  CA  VAL A1218     121.641 178.231 172.872  1.00 13.11           C
ATOM  14749  C   VAL A1218     121.170 179.186 171.783  1.00 13.11           C
ATOM  14750  O   VAL A1218     120.295 178.848 170.975  1.00 13.11           O
ATOM  14751  CB  VAL A1218     120.979 178.546 174.227  1.00 13.11           C
ATOM  14752  CG1 VAL A1218     119.471 178.670 174.069  1.00 13.11           C
ATOM  14753  CG2 VAL A1218     121.317 177.469 175.246  1.00 13.11           C
ATOM  14754  H   VAL A1218     123.382 178.556 173.757  1.00 13.11           H
ATOM  14755  HA  VAL A1218     121.376 177.334 172.615  1.00 13.11           H
ATOM  14756  HB  VAL A1218     121.319 179.392 174.558  1.00 13.11           H
ATOM  14757 HG11 VAL A1218     119.059 178.609 174.946  1.00 13.11           H
ATOM  14758 HG12 VAL A1218     119.262 179.528 173.666  1.00 13.11           H
ATOM  14759 HG13 VAL A1218     119.152 177.949 173.505  1.00 13.11           H
ATOM  14760 HG21 VAL A1218     121.057 177.777 176.128  1.00 13.11           H
ATOM  14761 HG22 VAL A1218     120.830 176.661 175.021  1.00 13.11           H
ATOM  14762 HG23 VAL A1218     122.270 177.296 175.224  1.00 13.11           H
ATOM  14763  N   LEU A1219     121.733 180.396 171.749  1.00 15.91           N
ATOM  14764  CA  LEU A1219     121.347 181.356 170.721  1.00 15.91           C
ATOM  14765  C   LEU A1219     121.670 180.828 169.329  1.00 15.91           C
ATOM  14766  O   LEU A1219     120.849 180.934 168.408  1.00 15.91           O
ATOM  14767  CB  LEU A1219     122.053 182.693 170.959  1.00 15.91           C
ATOM  14768  CG  LEU A1219     121.456 183.655 171.994  1.00 15.91           C
ATOM  14769  CD1 LEU A1219     122.156 185.005 171.920  1.00 15.91           C
ATOM  14770  CD2 LEU A1219     119.954 183.831 171.817  1.00 15.91           C
ATOM  14771  H   LEU A1219     122.329 180.679 172.301  1.00 15.91           H
ATOM  14772  HA  LEU A1219     120.389 181.496 170.764  1.00 15.91           H
ATOM  14773  HB2 LEU A1219     122.961 182.503 171.242  1.00 15.91           H
ATOM  14774  HB3 LEU A1219     122.079 183.170 170.115  1.00 15.91           H
ATOM  14775  HG  LEU A1219     121.609 183.292 172.881  1.00 15.91           H
ATOM  14776 HD11 LEU A1219     121.810 185.578 172.622  1.00 15.91           H
ATOM  14777 HD12 LEU A1219     123.110 184.874 172.040  1.00 15.91           H
ATOM  14778 HD13 LEU A1219     121.983 185.403 171.053  1.00 15.91           H
ATOM  14779 HD21 LEU A1219     119.666 184.605 172.326  1.00 15.91           H
ATOM  14780 HD22 LEU A1219     119.760 183.965 170.876  1.00 15.91           H
ATOM  14781 HD23 LEU A1219     119.501 183.037 172.139  1.00 15.91           H
ATOM  14782  N   LYS A1220     122.863 180.252 169.154  1.00 15.12           N
ATOM  14783  CA  LYS A1220     123.227 179.732 167.840  1.00 15.12           C
ATOM  14784  C   LYS A1220     122.334 178.566 167.433  1.00 15.12           C
ATOM  14785  O   LYS A1220     121.964 178.453 166.258  1.00 15.12           O
ATOM  14786  CB  LYS A1220     124.697 179.314 167.821  1.00 15.12           C
ATOM  14787  CG  LYS A1220     125.665 180.487 167.891  1.00 15.12           C
ATOM  14788  CD  LYS A1220     127.107 180.022 168.002  1.00 15.12           C
ATOM  14789  CE  LYS A1220     127.593 179.402 166.702  1.00 15.12           C
ATOM  14790  NZ  LYS A1220     129.047 179.090 166.743  1.00 15.12           N
ATOM  14791  H   LYS A1220     123.461 180.151 169.764  1.00 15.12           H
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ATOM  14792  HA  LYS A1220     123.111 180.436 167.183  1.00 15.12        H
ATOM  14793  HB2 LYS A1220     124.870 178.740 168.584  1.00 15.12        H
ATOM  14794  HB3 LYS A1220     124.873 178.832 166.999  1.00 15.12        H
ATOM  14795  HG2 LYS A1220     125.579 181.020 167.085  1.00 15.12        H
ATOM  14796  HG3 LYS A1220     125.459 181.026 168.671  1.00 15.12        H
ATOM  14797  HD2 LYS A1220     127.674 180.781 168.208  1.00 15.12        H
ATOM  14798  HD3 LYS A1220     127.174 179.353 168.701  1.00 15.12        H
ATOM  14799  HE2 LYS A1220     127.110 178.578 166.538  1.00 15.12        H
ATOM  14800  HE3 LYS A1220     127.440 180.027 165.977  1.00 15.12        H
ATOM  14801  HZ1 LYS A1220     129.292 178.683 165.990  1.00 15.12        H
ATOM  14802  HZ2 LYS A1220     129.517 179.840 166.833  1.00 15.12        H
ATOM  14803  HZ3 LYS A1220     129.223 178.554 167.432  1.00 15.12        H
ATOM  14804  N   LEU A1221     121.979 177.693 168.379  1.00 15.41        N
ATOM  14805  CA  LEU A1221     121.044 176.615 168.070  1.00 15.41        C
ATOM  14806  C   LEU A1221     119.698 177.174 167.628  1.00 15.41        C
ATOM  14807  O   LEU A1221     119.147 176.749 166.603  1.00 15.41        O
ATOM  14808  CB  LEU A1221     120.867 175.709 169.290  1.00 15.41        C
ATOM  14809  CG  LEU A1221     121.749 174.462 169.390  1.00 15.41        C
ATOM  14810  CD1 LEU A1221     121.500 173.750 170.710  1.00 15.41        C
ATOM  14811  CD2 LEU A1221     121.494 173.517 168.228  1.00 15.41        C
ATOM  14812  H   LEU A1221     122.258 177.705 169.192  1.00 15.41        H
ATOM  14813  HA  LEU A1221     121.403 176.086 167.342  1.00 15.41        H
ATOM  14814  HB2 LEU A1221     121.031 176.239 170.086  1.00 15.41        H
ATOM  14815  HB3 LEU A1221     119.946 175.403 169.299  1.00 15.41        H
ATOM  14816  HG  LEU A1221     122.681 174.729 169.363  1.00 15.41        H
ATOM  14817 HD11 LEU A1221     122.027 172.936 170.734  1.00 15.41        H
ATOM  14818 HD12 LEU A1221     121.761 174.335 171.439  1.00 15.41        H
ATOM  14819 HD13 LEU A1221     120.556 173.535 170.780  1.00 15.41        H
ATOM  14820 HD21 LEU A1221     121.939 172.673 168.405  1.00 15.41        H
ATOM  14821 HD22 LEU A1221     120.538 173.374 168.144  1.00 15.41        H
ATOM  14822 HD23 LEU A1221     121.843 173.910 167.413  1.00 15.41        H
ATOM  14823  N   ILE A1222     119.169 178.147 168.375  1.00 19.75        N
ATOM  14824  CA  ILE A1222     117.889 178.750 168.017  1.00 19.75        C
ATOM  14825  C   ILE A1222     117.957 179.321 166.610  1.00 19.75        C
ATOM  14826  O   ILE A1222     117.017 179.184 165.818  1.00 19.75        O
ATOM  14827  CB  ILE A1222     117.506 179.836 169.040  1.00 19.75        C
ATOM  14828  CG1 ILE A1222     116.986 179.201 170.329  1.00 19.75        C
ATOM  14829  CG2 ILE A1222     116.460 180.782 168.456  1.00 19.75        C
ATOM  14830  CD1 ILE A1222     117.263 180.034 171.559  1.00 19.75        C
ATOM  14831  H   ILE A1222     119.530 178.472 169.084  1.00 19.75        H
ATOM  14832  HA  ILE A1222     117.201 178.067 168.032  1.00 19.75        H
ATOM  14833  HB  ILE A1222     118.300 180.351 169.251  1.00 19.75        H
ATOM  14834 HG12 ILE A1222     116.026 179.084 170.258  1.00 19.75        H
ATOM  14835 HG13 ILE A1222     117.417 178.341 170.450  1.00 19.75        H
ATOM  14836 HG21 ILE A1222     116.040 181.270 169.182  1.00 19.75        H
ATOM  14837 HG22 ILE A1222     116.894 181.406 167.852  1.00 19.75        H
ATOM  14838 HG23 ILE A1222     115.793 180.264 167.980  1.00 19.75        H
ATOM  14839 HD11 ILE A1222     116.912 179.574 172.338  1.00 19.75        H
ATOM  14840 HD12 ILE A1222     118.222 180.155 171.649  1.00 19.75        H
ATOM  14841 HD13 ILE A1222     116.830 180.896 171.459  1.00 19.75        H
ATOM  14842  N   SER A1223     119.068 179.979 166.282  1.00 21.08        N
ATOM  14843  CA  SER A1223     119.190 180.609 164.973  1.00 21.08        C
ATOM  14844  C   SER A1223     119.260 179.572 163.857  1.00 21.08        C
ATOM  14845  O   SER A1223     118.573 179.700 162.837  1.00 21.08        O
ATOM  14846  CB  SER A1223     120.422 181.513 164.944  1.00 21.08        C
ATOM  14847  OG  SER A1223     120.075 182.848 165.264  1.00 21.08        O
ATOM  14848  H   SER A1223     119.753 180.074 166.792  1.00 21.08        H
ATOM  14849  HA  SER A1223     118.410 181.162 164.816  1.00 21.08        H
ATOM  14850  HB2 SER A1223     121.069 181.191 165.591  1.00 21.08        H
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ATOM  14851  HB3 SER A1223     120.806 181.494 164.053  1.00 21.08        H
ATOM  14852  HG  SER A1223     120.768 183.321 165.317  1.00 21.08        H
ATOM  14853  N   LEU A1224     120.080 178.534 164.031  1.00 20.02        N
ATOM  14854  CA  LEU A1224     120.460 177.701 162.896  1.00 20.02        C
ATOM  14855  C   LEU A1224     119.635 176.427 162.744  1.00 20.02        C
ATOM  14856  O   LEU A1224     119.672 175.827 161.666  1.00 20.02        O
ATOM  14857  CB  LEU A1224     121.947 177.346 162.986  1.00 20.02        C
ATOM  14858  CG  LEU A1224     122.858 178.579 163.035  1.00 20.02        C
ATOM  14859  CD1 LEU A1224     124.236 178.225 163.552  1.00 20.02        C
ATOM  14860  CD2 LEU A1224     122.951 179.244 161.669  1.00 20.02        C
ATOM  14861  H   LEU A1224     120.425 178.297 164.782  1.00 20.02        H
ATOM  14862  HA  LEU A1224     120.334 178.217 162.085  1.00 20.02        H
ATOM  14863  HB2 LEU A1224     122.103 176.828 163.791  1.00 20.02        H
ATOM  14864  HB3 LEU A1224     122.193 176.827 162.204  1.00 20.02        H
ATOM  14865  HG  LEU A1224     122.478 179.224 163.651  1.00 20.02        H
ATOM  14866 HD11 LEU A1224     124.791 179.021 163.538  1.00 20.02        H
ATOM  14867 HD12 LEU A1224     124.148 177.900 164.460  1.00 20.02        H
ATOM  14868 HD13 LEU A1224     124.625 177.539 162.986  1.00 20.02        H
ATOM  14869 HD21 LEU A1224     123.292 180.145 161.778  1.00 20.02        H
ATOM  14870 HD22 LEU A1224     123.549 178.732 161.102  1.00 20.02        H
ATOM  14871 HD23 LEU A1224     122.068 179.275 161.274  1.00 20.02        H
ATOM  14872  N   ARG A1225     118.897 175.990 163.769  1.00 23.58        N
ATOM  14873  CA  ARG A1225     117.881 174.941 163.601  1.00 23.58        C
ATOM  14874  C   ARG A1225     118.377 173.761 162.762  1.00 23.58        C
ATOM  14875  O   ARG A1225     117.921 173.576 161.634  1.00 23.58        O
ATOM  14876  CB  ARG A1225     116.613 175.505 162.956  1.00 23.58        C
ATOM  14877  CG  ARG A1225     116.032 176.739 163.619  1.00 23.58        C
ATOM  14878  CD  ARG A1225     115.429 177.653 162.567  1.00 23.58        C
ATOM  14879  NE  ARG A1225     116.429 178.057 161.579  1.00 23.58        N
ATOM  14880  CZ  ARG A1225     116.165 178.375 160.315  1.00 23.58        C
ATOM  14881  NH1 ARG A1225     114.924 178.325 159.851  1.00 23.58        N
ATOM  14882  NH2 ARG A1225     117.154 178.732 159.507  1.00 23.58        N
ATOM  14883  H   ARG A1225     118.961 176.288 164.573  1.00 23.58        H
ATOM  14884  HA  ARG A1225     117.641 174.599 164.476  1.00 23.58        H
ATOM  14885  HB2 ARG A1225     116.814 175.720 162.033  1.00 23.58        H
ATOM  14886  HB3 ARG A1225     115.931 174.816 162.981  1.00 23.58        H
ATOM  14887  HG2 ARG A1225     115.331 176.475 164.236  1.00 23.58        H
ATOM  14888  HG3 ARG A1225     116.729 177.224 164.087  1.00 23.58        H
ATOM  14889  HD2 ARG A1225     114.720 177.175 162.109  1.00 23.58        H
ATOM  14890  HD3 ARG A1225     115.078 178.451 162.992  1.00 23.58        H
ATOM  14891  HE  ARG A1225     117.257 178.002 161.808  1.00 23.58        H
ATOM  14892 HH11 ARG A1225     114.275 178.096 160.365  1.00 23.58        H
ATOM  14893 HH12 ARG A1225     114.768 178.531 159.030  1.00 23.58        H
ATOM  14894 HH21 ARG A1225     117.961 178.763 159.803  1.00 23.58        H
ATOM  14895 HH22 ARG A1225     116.988 178.934 158.688  1.00 23.58        H
ATOM  14896  N   HIS A1226     119.328 172.985 163.277  1.00 21.12        N
ATOM  14897  CA  HIS A1226     119.819 171.756 162.652  1.00 21.12        C
ATOM  14898  C   HIS A1226     120.754 172.054 161.484  1.00 21.12        C
ATOM  14899  O   HIS A1226     121.369 171.135 160.933  1.00 21.12        O
ATOM  14900  CB  HIS A1226     118.667 170.856 162.173  1.00 21.12        C
ATOM  14901  CG  HIS A1226     118.364 170.962 160.706  1.00 21.12        C
ATOM  14902  ND1 HIS A1226     119.172 170.401 159.739  1.00 21.12        N
ATOM  14903  CD2 HIS A1226     117.316 171.510 160.044  1.00 21.12        C
ATOM  14904  CE1 HIS A1226     118.657 170.635 158.546  1.00 21.12        C
ATOM  14905  NE2 HIS A1226     117.531 171.306 158.703  1.00 21.12        N
ATOM  14906  H   HIS A1226     119.722 173.160 164.021  1.00 21.12        H
ATOM  14907  HA  HIS A1226     120.326 171.257 163.311  1.00 21.12        H
ATOM  14908  HB2 HIS A1226     118.897 169.932 162.357  1.00 21.12        H
ATOM  14909  HB3 HIS A1226     117.862 171.093 162.657  1.00 21.12        H
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ATOM  14910  HD2 HIS A1226     116.599 171.963 160.425  1.00 21.12        H
ATOM  14911  HE1 HIS A1226     119.020 170.366 157.733  1.00 21.12        H
ATOM  14912  HE2 HIS A1226     117.012 171.567 158.067  1.00 21.12        H
ATOM  14913  N   TYR A1227     120.880 173.326 161.101  1.00 21.95        N
ATOM  14914  CA  TYR A1227     122.022 173.730 160.292  1.00 21.95        C
ATOM  14915  C   TYR A1227     123.251 173.946 161.162  1.00 21.95        C
ATOM  14916  O   TYR A1227     124.363 174.067 160.636  1.00 21.95        O
ATOM  14917  CB  TYR A1227     121.704 175.002 159.501  1.00 21.95        C
ATOM  14918  CG  TYR A1227     120.583 174.866 158.486  1.00 21.95        C
ATOM  14919  CD1 TYR A1227     120.838 174.400 157.202  1.00 21.95        C
ATOM  14920  CD2 TYR A1227     119.278 175.230 158.799  1.00 21.95        C
ATOM  14921  CE1 TYR A1227     119.825 174.282 156.268  1.00 21.95        C
ATOM  14922  CE2 TYR A1227     118.259 175.116 157.869  1.00 21.95        C
ATOM  14923  CZ  TYR A1227     118.539 174.643 156.606  1.00 21.95        C
ATOM  14924  OH  TYR A1227     117.529 174.528 155.677  1.00 21.95        O
ATOM  14925  H   TYR A1227     120.332 173.960 161.287  1.00 21.95        H
ATOM  14926  HA  TYR A1227     122.223 173.026 159.656  1.00 21.95        H
ATOM  14927  HB2 TYR A1227     121.455 175.702 160.124  1.00 21.95        H
ATOM  14928  HB3 TYR A1227     122.502 175.268 159.018  1.00 21.95        H
ATOM  14929  HD1 TYR A1227     121.704 174.154 156.970  1.00 21.95        H
ATOM  14930  HD2 TYR A1227     119.081 175.550 159.647  1.00 21.95        H
ATOM  14931  HE1 TYR A1227     120.012 173.963 155.414  1.00 21.95        H
ATOM  14932  HE2 TYR A1227     117.390 175.359 158.095  1.00 21.95        H
ATOM  14933  HH  TYR A1227     116.822 174.868 155.977  1.00 21.95        H
ATOM  14934  N   TYR A1228     123.062 173.987 162.484  1.00 14.63        N
ATOM  14935  CA  TYR A1228     124.162 174.214 163.414  1.00 14.63        C
ATOM  14936  C   TYR A1228     125.209 173.111 163.331  1.00 14.63        C
ATOM  14937  O   TYR A1228     126.413 173.379 163.408  1.00 14.63        O
ATOM  14938  CB  TYR A1228     123.603 174.311 164.836  1.00 14.63        C
ATOM  14939  CG  TYR A1228     124.641 174.526 165.913  1.00 14.63        C
ATOM  14940  CD1 TYR A1228     125.119 175.795 166.200  1.00 14.63        C
ATOM  14941  CD2 TYR A1228     125.136 173.457 166.649  1.00 14.63        C
ATOM  14942  CE1 TYR A1228     126.062 175.997 167.186  1.00 14.63        C
ATOM  14943  CE2 TYR A1228     126.081 173.649 167.637  1.00 14.63        C
ATOM  14944  CZ  TYR A1228     126.541 174.921 167.901  1.00 14.63        C
ATOM  14945  OH  TYR A1228     127.483 175.118 168.884  1.00 14.63        O
ATOM  14946  H   TYR A1228     122.300 173.886 162.868  1.00 14.63        H
ATOM  14947  HA  TYR A1228     124.592 175.056 163.200  1.00 14.63        H
ATOM  14948  HB2 TYR A1228     122.982 175.055 164.875  1.00 14.63        H
ATOM  14949  HB3 TYR A1228     123.134 173.486 165.041  1.00 14.63        H
ATOM  14950  HD1 TYR A1228     124.797 176.522 165.721  1.00 14.63        H
ATOM  14951  HD2 TYR A1228     124.828 172.598 166.472  1.00 14.63        H
ATOM  14952  HE1 TYR A1228     126.374 176.854 167.367  1.00 14.63        H
ATOM  14953  HE2 TYR A1228     126.407 172.925 168.121  1.00 14.63        H
ATOM  14954  HH  TYR A1228     127.682 174.384 169.241  1.00 14.63        H
ATOM  14955  N   PHE A1229     124.769 171.864 163.178  1.00 14.80        N
ATOM  14956  CA  PHE A1229     125.660 170.715 163.278  1.00 14.80        C
ATOM  14957  C   PHE A1229     126.379 170.390 161.975  1.00 14.80        C
ATOM  14958  O   PHE A1229     127.139 169.417 161.936  1.00 14.80        O
ATOM  14959  CB  PHE A1229     124.874 169.491 163.752  1.00 14.80        C
ATOM  14960  CG  PHE A1229     124.277 169.653 165.119  1.00 14.80        C
ATOM  14961  CD1 PHE A1229     125.065 169.531 166.251  1.00 14.80        C
ATOM  14962  CD2 PHE A1229     122.931 169.938 165.273  1.00 14.80        C
ATOM  14963  CE1 PHE A1229     124.520 169.684 167.511  1.00 14.80        C
ATOM  14964  CE2 PHE A1229     122.380 170.091 166.530  1.00 14.80        C
ATOM  14965  CZ  PHE A1229     123.176 169.964 167.650  1.00 14.80        C
ATOM  14966  H   PHE A1229     123.951 171.656 163.013  1.00 14.80        H
ATOM  14967  HA  PHE A1229     126.337 170.907 163.946  1.00 14.80        H
ATOM  14968  HB2 PHE A1229     124.149 169.324 163.129  1.00 14.80        H
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ATOM  14969  HB3 PHE A1229     125.470 168.726 163.777  1.00 14.80           H
ATOM  14970  HD1 PHE A1229     125.971 169.343 166.163  1.00 14.80           H
ATOM  14971  HD2 PHE A1229     122.391 170.024 164.520  1.00 14.80           H
ATOM  14972  HE1 PHE A1229     125.058 169.598 168.265  1.00 14.80           H
ATOM  14973  HE2 PHE A1229     121.474 170.280 166.621  1.00 14.80           H
ATOM  14974  HZ  PHE A1229     122.807 170.067 168.498  1.00 14.80           H
ATOM  14975  N   THR A1230     126.157 171.160 160.909  1.00 16.95           N
ATOM  14976  CA  THR A1230     126.917 170.940 159.684  1.00 16.95           C
ATOM  14977  C   THR A1230     128.359 171.415 159.827  1.00 16.95           C
ATOM  14978  O   THR A1230     129.239 170.946 159.097  1.00 16.95           O
ATOM  14979  CB  THR A1230     126.242 171.645 158.507  1.00 16.95           C
ATOM  14980  OG1 THR A1230     126.177 173.055 158.760  1.00 16.95           O
ATOM  14981  CG2 THR A1230     124.836 171.100 158.290  1.00 16.95           C
ATOM  14982  H   THR A1230     125.585 171.801 160.869  1.00 16.95           H
ATOM  14983  HA  THR A1230     126.935 169.989 159.490  1.00 16.95           H
ATOM  14984  HB  THR A1230     126.756 171.487 157.700  1.00 16.95           H
ATOM  14985  HG1 THR A1230     125.830 173.448 158.104  1.00 16.95           H
ATOM  14986 HG21 THR A1230     124.427 171.536 157.527  1.00 16.95           H
ATOM  14987 HG22 THR A1230     124.874 170.145 158.124  1.00 16.95           H
ATOM  14988 HG23 THR A1230     124.290 171.262 159.076  1.00 16.95           H
ATOM  14989  N   VAL A1231     128.618 172.332 160.756  1.00 13.54           N
ATOM  14990  CA  VAL A1231     129.953 172.876 160.973  1.00 13.54           C
ATOM  14991  C   VAL A1231     130.625 172.096 162.097  1.00 13.54           C
ATOM  14992  O   VAL A1231     130.032 171.889 163.163  1.00 13.54           O
ATOM  14993  CB  VAL A1231     129.884 174.376 161.307  1.00 13.54           C
ATOM  14994  CG1 VAL A1231     131.281 174.975 161.385  1.00 13.54           C
ATOM  14995  CG2 VAL A1231     129.031 175.112 160.278  1.00 13.54           C
ATOM  14996  H   VAL A1231     128.023 172.662 161.283  1.00 13.54           H
ATOM  14997  HA  VAL A1231     130.481 172.768 160.167  1.00 13.54           H
ATOM  14998  HB  VAL A1231     129.464 174.486 162.174  1.00 13.54           H
ATOM  14999 HG11 VAL A1231     131.205 175.936 161.501  1.00 13.54           H
ATOM  15000 HG12 VAL A1231     131.752 174.588 162.139  1.00 13.54           H
ATOM  15001 HG13 VAL A1231     131.754 174.780 160.561  1.00 13.54           H
ATOM  15002 HG21 VAL A1231     129.087 176.066 160.446  1.00 13.54           H
ATOM  15003 HG22 VAL A1231     129.364 174.912 159.390  1.00 13.54           H
ATOM  15004 HG23 VAL A1231     128.111 174.816 160.360  1.00 13.54           H
ATOM  15005  N   GLY A1232     131.863 171.658 161.859  1.00 11.45           N
ATOM  15006  CA  GLY A1232     132.557 170.850 162.850  1.00 11.45           C
ATOM  15007  C   GLY A1232     132.891 171.616 164.118  1.00 11.45           C
ATOM  15008  O   GLY A1232     132.763 171.086 165.227  1.00 11.45           O
ATOM  15009  H   GLY A1232     132.314 171.815 161.143  1.00 11.45           H
ATOM  15010  HA2 GLY A1232     132.000 170.093 163.091  1.00 11.45           H
ATOM  15011  HA3 GLY A1232     133.383 170.512 162.470  1.00 11.45           H
ATOM  15012  N   TRP A1233     133.333 172.867 163.974  1.00  9.40           N
ATOM  15013  CA  TRP A1233     133.640 173.672 165.151  1.00  9.40           C
ATOM  15014  C   TRP A1233     132.402 173.858 166.017  1.00  9.40           C
ATOM  15015  O   TRP A1233     132.495 173.901 167.250  1.00  9.40           O
ATOM  15016  CB  TRP A1233     134.209 175.028 164.732  1.00  9.40           C
ATOM  15017  CG  TRP A1233     135.703 175.037 164.583  1.00  9.40           C
ATOM  15018  CD1 TRP A1233     136.412 175.032 163.417  1.00  9.40           C
ATOM  15019  CD2 TRP A1233     136.671 175.048 165.640  1.00  9.40           C
ATOM  15020  NE1 TRP A1233     137.759 175.044 163.682  1.00  9.40           N
ATOM  15021  CE2 TRP A1233     137.945 175.054 165.039  1.00  9.40           C
ATOM  15022  CE3 TRP A1233     136.583 175.058 167.036  1.00  9.40           C
ATOM  15023  CZ2 TRP A1233     139.122 175.067 165.785  1.00  9.40           C
ATOM  15024  CZ3 TRP A1233     137.753 175.071 167.774  1.00  9.40           C
ATOM  15025  CH2 TRP A1233     139.005 175.075 167.148  1.00  9.40           C
ATOM  15026  H   TRP A1233     133.460 173.264 163.222  1.00  9.40           H
ATOM  15027  HA  TRP A1233     134.311 173.215 165.682  1.00  9.40           H
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ATOM  15028  HB2 TRP A1233     133.824 175.282 163.879  1.00  9.40           H
ATOM  15029  HB3 TRP A1233     133.973 175.682 165.406  1.00  9.40           H
ATOM  15030  HD1 TRP A1233     136.038 175.024 162.566  1.00  9.40           H
ATOM  15031  HE1 TRP A1233     138.385 175.043 163.092  1.00  9.40           H
ATOM  15032  HE3 TRP A1233     135.755 175.056 167.458  1.00  9.40           H
ATOM  15033  HZ2 TRP A1233     139.956 175.069 165.372  1.00  9.40           H
ATOM  15034  HZ3 TRP A1233     137.708 175.077 168.703  1.00  9.40           H
ATOM  15035  HH2 TRP A1233     139.775 175.084 167.670  1.00  9.40           H
ATOM  15036  N   ASN A1234     131.231 173.972 165.388  1.00 11.66           N
ATOM  15037  CA  ASN A1234     129.991 174.060 166.151  1.00 11.66           C
ATOM  15038  C   ASN A1234     129.776 172.803 166.984  1.00 11.66           C
ATOM  15039  O   ASN A1234     129.358 172.882 168.145  1.00 11.66           O
ATOM  15040  CB  ASN A1234     128.814 174.288 165.203  1.00 11.66           C
ATOM  15041  CG  ASN A1234     128.684 175.737 164.776  1.00 11.66           C
ATOM  15042  OD1 ASN A1234     129.596 176.538 164.976  1.00 11.66           O
ATOM  15043  ND2 ASN A1234     127.549 176.079 164.178  1.00 11.66           N
ATOM  15044  H   ASN A1234     131.130 174.000 164.535  1.00 11.66           H
ATOM  15045  HA  ASN A1234     130.043 174.816 166.756  1.00 11.66           H
ATOM  15046  HB2 ASN A1234     128.942 173.751 164.405  1.00 11.66           H
ATOM  15047  HB3 ASN A1234     127.993 174.031 165.648  1.00 11.66           H
ATOM  15048 HD21 ASN A1234     126.933 175.491 164.054  1.00 11.66           H
ATOM  15049 HD22 ASN A1234     127.429 176.889 163.917  1.00 11.66           H
ATOM  15050  N   ILE A1235     130.068 171.634 166.412  1.00  8.89           N
ATOM  15051  CA  ILE A1235     129.938 170.387 167.160  1.00  8.89           C
ATOM  15052  C   ILE A1235     130.919 170.364 168.325  1.00  8.89           C
ATOM  15053  O   ILE A1235     130.581 169.923 169.431  1.00  8.89           O
ATOM  15054  CB  ILE A1235     130.144 169.179 166.227  1.00  8.89           C
ATOM  15055  CG1 ILE A1235     129.126 169.200 165.083  1.00  8.89           C
ATOM  15056  CG2 ILE A1235     130.036 167.876 167.008  1.00  8.89           C
ATOM  15057  CD1 ILE A1235     129.514 168.322 163.913  1.00  8.89           C
ATOM  15058  H   ILE A1235     130.343 171.538 165.603  1.00  8.89           H
ATOM  15059  HA  ILE A1235     129.041 170.332 167.524  1.00  8.89           H
ATOM  15060  HB  ILE A1235     131.034 169.235 165.845  1.00  8.89           H
ATOM  15061 HG12 ILE A1235     128.271 168.888 165.420  1.00  8.89           H
ATOM  15062 HG13 ILE A1235     129.036 170.106 164.751  1.00  8.89           H
ATOM  15063 HG21 ILE A1235     129.997 167.135 166.383  1.00  8.89           H
ATOM  15064 HG22 ILE A1235     130.814 167.781 167.579  1.00  8.89           H
ATOM  15065 HG23 ILE A1235     129.229 167.896 167.546  1.00  8.89           H
ATOM  15066 HD11 ILE A1235     128.872 168.446 163.198  1.00  8.89           H
ATOM  15067 HD12 ILE A1235     130.399 168.575 163.610  1.00  8.89           H
ATOM  15068 HD13 ILE A1235     129.514 167.395 164.199  1.00  8.89           H
ATOM  15069  N   PHE A1236     132.151 170.822 168.094  1.00  7.21           N
ATOM  15070  CA  PHE A1236     133.133 170.848 169.175  1.00  7.21           C
ATOM  15071  C   PHE A1236     132.674 171.757 170.311  1.00  7.21           C
ATOM  15072  O   PHE A1236     132.779 171.392 171.489  1.00  7.21           O
ATOM  15073  CB  PHE A1236     134.490 171.299 168.635  1.00  7.21           C
ATOM  15074  CG  PHE A1236     135.553 171.414 169.688  1.00  7.21           C
ATOM  15075  CD1 PHE A1236     136.267 170.298 170.092  1.00  7.21           C
ATOM  15076  CD2 PHE A1236     135.845 172.636 170.270  1.00  7.21           C
ATOM  15077  CE1 PHE A1236     137.247 170.398 171.059  1.00  7.21           C
ATOM  15078  CE2 PHE A1236     136.824 172.742 171.237  1.00  7.21           C
ATOM  15079  CZ  PHE A1236     137.526 171.622 171.633  1.00  7.21           C
ATOM  15080  H   PHE A1236     132.436 171.118 167.339  1.00  7.21           H
ATOM  15081  HA  PHE A1236     133.234 169.952 169.531  1.00  7.21           H
ATOM  15082  HB2 PHE A1236     134.793 170.656 167.975  1.00  7.21           H
ATOM  15083  HB3 PHE A1236     134.387 172.171 168.222  1.00  7.21           H
ATOM  15084  HD1 PHE A1236     136.081 169.471 169.709  1.00  7.21           H
ATOM  15085  HD2 PHE A1236     135.374 173.394 170.007  1.00  7.21           H
ATOM  15086  HE1 PHE A1236     137.719 169.642 171.324  1.00  7.21           H
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ATOM  15087  HE2 PHE A1236     137.011 173.568 171.622  1.00  7.21           H
ATOM  15088  HZ  PHE A1236     138.187 171.691 172.284  1.00  7.21           H
ATOM  15089  N   ASP A1237     132.150 172.938 169.976  1.00 10.05           N
ATOM  15090  CA  ASP A1237     131.661 173.850 171.008  1.00 10.05           C
ATOM  15091  C   ASP A1237     130.464 173.260 171.744  1.00 10.05           C
ATOM  15092  O   ASP A1237     130.332 173.423 172.962  1.00 10.05           O
ATOM  15093  CB  ASP A1237     131.300 175.202 170.391  1.00 10.05           C
ATOM  15094  CG  ASP A1237     132.332 175.682 169.390  1.00 10.05           C
ATOM  15095  OD1 ASP A1237     133.470 175.167 169.416  1.00 10.05           O
ATOM  15096  OD2 ASP A1237     132.007 176.571 168.575  1.00 10.05           O
ATOM  15097  H   ASP A1237     132.064 173.225 169.170  1.00 10.05           H
ATOM  15098  HA  ASP A1237     132.367 173.997 171.656  1.00 10.05           H
ATOM  15099  HB2 ASP A1237     130.450 175.123 169.930  1.00 10.05           H
ATOM  15100  HB3 ASP A1237     131.235 175.865 171.096  1.00 10.05           H
ATOM  15101  N   PHE A1238     129.575 172.578 171.019  1.00  8.65           N
ATOM  15102  CA  PHE A1238     128.428 171.932 171.650  1.00  8.65           C
ATOM  15103  C   PHE A1238     128.881 170.874 172.652  1.00  8.65           C
ATOM  15104  O   PHE A1238     128.372 170.801 173.781  1.00  8.65           O
ATOM  15105  CB  PHE A1238     127.548 171.319 170.558  1.00  8.65           C
ATOM  15106  CG  PHE A1238     126.298 170.667 171.066  1.00  8.65           C
ATOM  15107  CD1 PHE A1238     125.231 171.430 171.505  1.00  8.65           C
ATOM  15108  CD2 PHE A1238     126.180 169.288 171.077  1.00  8.65           C
ATOM  15109  CE1 PHE A1238     124.075 170.829 171.962  1.00  8.65           C
ATOM  15110  CE2 PHE A1238     125.027 168.681 171.530  1.00  8.65           C
ATOM  15111  CZ  PHE A1238     123.972 169.454 171.974  1.00  8.65           C
ATOM  15112  H   PHE A1238     129.615 172.477 170.166  1.00  8.65           H
ATOM  15113  HA  PHE A1238     127.906 172.597 172.125  1.00  8.65           H
ATOM  15114  HB2 PHE A1238     127.285 172.021 169.942  1.00  8.65           H
ATOM  15115  HB3 PHE A1238     128.062 170.645 170.086  1.00  8.65           H
ATOM  15116  HD1 PHE A1238     125.296 172.358 171.499  1.00  8.65           H
ATOM  15117  HD2 PHE A1238     126.889 168.763 170.779  1.00  8.65           H
ATOM  15118  HE1 PHE A1238     123.365 171.351 172.260  1.00  8.65           H
ATOM  15119  HE2 PHE A1238     124.961 167.754 171.538  1.00  8.65           H
ATOM  15120  HZ  PHE A1238     123.195 169.047 172.282  1.00  8.65           H
ATOM  15121  N   VAL A1239     129.852 170.049 172.253  1.00  6.89           N
ATOM  15122  CA  VAL A1239     130.386 169.031 173.152  1.00  6.89           C
ATOM  15123  C   VAL A1239     131.019 169.685 174.371  1.00  6.89           C
ATOM  15124  O   VAL A1239     130.845 169.221 175.506  1.00  6.89           O
ATOM  15125  CB  VAL A1239     131.392 168.135 172.406  1.00  6.89           C
ATOM  15126  CG1 VAL A1239     132.161 167.259 173.386  1.00  6.89           C
ATOM  15127  CG2 VAL A1239     130.677 167.281 171.370  1.00  6.89           C
ATOM  15128  H   VAL A1239     130.215 170.061 171.473  1.00  6.89           H
ATOM  15129  HA  VAL A1239     129.657 168.469 173.459  1.00  6.89           H
ATOM  15130  HB  VAL A1239     132.031 168.697 171.941  1.00  6.89           H
ATOM  15131 HG11 VAL A1239     132.550 166.514 172.902  1.00  6.89           H
ATOM  15132 HG12 VAL A1239     132.864 167.786 173.798  1.00  6.89           H
ATOM  15133 HG13 VAL A1239     131.550 166.929 174.063  1.00  6.89           H
ATOM  15134 HG21 VAL A1239     131.334 166.750 170.892  1.00  6.89           H
ATOM  15135 HG22 VAL A1239     130.047 166.699 171.822  1.00  6.89           H
ATOM  15136 HG23 VAL A1239     130.207 167.862 170.752  1.00  6.89           H
ATOM  15137  N   VAL A1240     131.769 170.769 174.158  1.00  6.57           N
ATOM  15138  CA  VAL A1240     132.418 171.451 175.274  1.00  6.57           C
ATOM  15139  C   VAL A1240     131.376 171.994 176.244  1.00  6.57           C
ATOM  15140  O   VAL A1240     131.548 171.918 177.464  1.00  6.57           O
ATOM  15141  CB  VAL A1240     133.345 172.566 174.754  1.00  6.57           C
ATOM  15142  CG1 VAL A1240     133.720 173.519 175.881  1.00  6.57           C
ATOM  15143  CG2 VAL A1240     134.591 171.965 174.123  1.00  6.57           C
ATOM  15144  H   VAL A1240     131.915 171.123 173.388  1.00  6.57           H
ATOM  15145  HA  VAL A1240     132.965 170.811 175.755  1.00  6.57           H
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ATOM  15146  HB  VAL A1240     132.878 173.074 174.073  1.00  6.57           H
ATOM  15147 HG11 VAL A1240     134.505 174.023 175.615  1.00  6.57           H
ATOM  15148 HG12 VAL A1240     132.981 174.126 176.046  1.00  6.57           H
ATOM  15149 HG13 VAL A1240     133.915 173.004 176.679  1.00  6.57           H
ATOM  15150 HG21 VAL A1240     135.142 172.681 173.770  1.00  6.57           H
ATOM  15151 HG22 VAL A1240     135.082 171.473 174.801  1.00  6.57           H
ATOM  15152 HG23 VAL A1240     134.326 171.367 173.407  1.00  6.57           H
ATOM  15153  N   VAL A1241     130.285 172.558 175.721  1.00  7.29           N
ATOM  15154  CA  VAL A1241     129.245 173.112 176.586  1.00  7.29           C
ATOM  15155  C   VAL A1241     128.587 172.010 177.410  1.00  7.29           C
ATOM  15156  O   VAL A1241     128.350 172.168 178.618  1.00  7.29           O
ATOM  15157  CB  VAL A1241     128.210 173.883 175.745  1.00  7.29           C
ATOM  15158  CG1 VAL A1241     126.965 174.184 176.568  1.00  7.29           C
ATOM  15159  CG2 VAL A1241     128.819 175.166 175.203  1.00  7.29           C
ATOM  15160  H   VAL A1241     130.126 172.630 174.879  1.00  7.29           H
ATOM  15161  HA  VAL A1241     129.653 173.740 177.203  1.00  7.29           H
ATOM  15162  HB  VAL A1241     127.946 173.334 174.990  1.00  7.29           H
ATOM  15163 HG11 VAL A1241     126.467 174.893 176.133  1.00  7.29           H
ATOM  15164 HG12 VAL A1241     126.418 173.385 176.624  1.00  7.29           H
ATOM  15165 HG13 VAL A1241     127.234 174.468 177.456  1.00  7.29           H
ATOM  15166 HG21 VAL A1241     128.184 175.587 174.603  1.00  7.29           H
ATOM  15167 HG22 VAL A1241     129.018 175.759 175.944  1.00  7.29           H
ATOM  15168 HG23 VAL A1241     129.634 174.951 174.724  1.00  7.29           H
ATOM  15169  N   ILE A1242     128.267 170.881 176.772  1.00  7.62           N
ATOM  15170  CA  ILE A1242     127.659 169.774 177.509  1.00  7.62           C
ATOM  15171  C   ILE A1242     128.606 169.287 178.600  1.00  7.62           C
ATOM  15172  O   ILE A1242     128.199 169.052 179.749  1.00  7.62           O
ATOM  15173  CB  ILE A1242     127.271 168.635 176.548  1.00  7.62           C
ATOM  15174  CG1 ILE A1242     125.909 168.920 175.916  1.00  7.62           C
ATOM  15175  CG2 ILE A1242     127.242 167.294 177.278  1.00  7.62           C
ATOM  15176  CD1 ILE A1242     125.667 168.162 174.638  1.00  7.62           C
ATOM  15177  H   ILE A1242     128.387 170.735 175.933  1.00  7.62           H
ATOM  15178  HA  ILE A1242     126.848 170.090 177.938  1.00  7.62           H
ATOM  15179  HB  ILE A1242     127.935 168.588 175.842  1.00  7.62           H
ATOM  15180 HG12 ILE A1242     125.214 168.672 176.546  1.00  7.62           H
ATOM  15181 HG13 ILE A1242     125.849 169.868 175.716  1.00  7.62           H
ATOM  15182 HG21 ILE A1242     126.767 166.650 176.729  1.00  7.62           H
ATOM  15183 HG22 ILE A1242     128.150 166.987 177.425  1.00  7.62           H
ATOM  15184 HG23 ILE A1242     126.781 167.401 178.125  1.00  7.62           H
ATOM  15185 HD11 ILE A1242     124.760 168.331 174.341  1.00  7.62           H
ATOM  15186 HD12 ILE A1242     126.301 168.465 173.969  1.00  7.62           H
ATOM  15187 HD13 ILE A1242     125.788 167.214 174.803  1.00  7.62           H
ATOM  15188  N   ILE A1243     129.884 169.123 178.253  1.00  8.15           N
ATOM  15189  CA  ILE A1243     130.865 168.669 179.232  1.00  8.15           C
ATOM  15190  C   ILE A1243     130.969 169.669 180.373  1.00  8.15           C
ATOM  15191  O   ILE A1243     131.125 169.286 181.534  1.00  8.15           O
ATOM  15192  CB  ILE A1243     132.230 168.438 178.559  1.00  8.15           C
ATOM  15193  CG1 ILE A1243     132.184 167.192 177.673  1.00  8.15           C
ATOM  15194  CG2 ILE A1243     133.323 168.295 179.607  1.00  8.15           C
ATOM  15195  CD1 ILE A1243     133.202 167.207 176.556  1.00  8.15           C
ATOM  15196  H   ILE A1243     130.203 169.266 177.467  1.00  8.15           H
ATOM  15197  HA  ILE A1243     130.569 167.824 179.603  1.00  8.15           H
ATOM  15198  HB  ILE A1243     132.434 169.205 178.002  1.00  8.15           H
ATOM  15199 HG12 ILE A1243     132.356 166.411 178.222  1.00  8.15           H
ATOM  15200 HG13 ILE A1243     131.303 167.125 177.271  1.00  8.15           H
ATOM  15201 HG21 ILE A1243     134.094 167.869 179.200  1.00  8.15           H
ATOM  15202 HG22 ILE A1243     133.568 169.175 179.935  1.00  8.15           H
ATOM  15203 HG23 ILE A1243     132.992 167.747 180.335  1.00  8.15           H
ATOM  15204 HD11 ILE A1243     133.051 166.441 175.980  1.00  8.15           H
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ATOM  15205 HD12 ILE A1243     133.102 168.028 176.049  1.00  8.15           H
ATOM  15206 HD13 ILE A1243     134.092 167.163 176.940  1.00  8.15           H
ATOM  15207  N   SER A1244     130.888 170.964 180.062  1.00  8.76           N
ATOM  15208  CA  SER A1244     130.985 171.982 181.102  1.00  8.76           C
ATOM  15209  C   SER A1244     129.810 171.901 182.067  1.00  8.76           C
ATOM  15210  O   SER A1244     129.993 172.020 183.282  1.00  8.76           O
ATOM  15211  CB  SER A1244     131.061 173.371 180.468  1.00  8.76           C
ATOM  15212  OG  SER A1244     132.214 173.497 179.655  1.00  8.76           O
ATOM  15213  H   SER A1244     130.779 171.273 179.267  1.00  8.76           H
ATOM  15214  HA  SER A1244     131.799 171.840 181.609  1.00  8.76           H
ATOM  15215  HB2 SER A1244     130.272 173.512 179.921  1.00  8.76           H
ATOM  15216  HB3 SER A1244     131.098 174.037 181.172  1.00  8.76           H
ATOM  15217  HG  SER A1244     132.236 174.260 179.305  1.00  8.76           H
ATOM  15218  N   ILE A1245     128.596 171.710 181.549  1.00  8.47           N
ATOM  15219  CA  ILE A1245     127.435 171.604 182.434  1.00  8.47           C
ATOM  15220  C   ILE A1245     127.560 170.371 183.326  1.00  8.47           C
ATOM  15221  O   ILE A1245     127.370 170.436 184.554  1.00  8.47           O
ATOM  15222  CB  ILE A1245     126.134 171.577 181.612  1.00  8.47           C
ATOM  15223  CG1 ILE A1245     125.874 172.949 180.987  1.00  8.47           C
ATOM  15224  CG2 ILE A1245     124.957 171.163 182.487  1.00  8.47           C
ATOM  15225  CD1 ILE A1245     124.911 172.917 179.821  1.00  8.47           C
ATOM  15226  H   ILE A1245     128.420 171.640 180.711  1.00  8.47           H
ATOM  15227  HA  ILE A1245     127.406 172.385 183.009  1.00  8.47           H
ATOM  15228  HB  ILE A1245     126.232 170.926 180.899  1.00  8.47           H
ATOM  15229 HG12 ILE A1245     125.500 173.534 181.664  1.00  8.47           H
ATOM  15230 HG13 ILE A1245     126.714 173.312 180.668  1.00  8.47           H
ATOM  15231 HG21 ILE A1245     124.132 171.425 182.050  1.00  8.47           H
ATOM  15232 HG22 ILE A1245     124.973 170.201 182.609  1.00  8.47           H
ATOM  15233 HG23 ILE A1245     125.030 171.610 183.345  1.00  8.47           H
ATOM  15234 HD11 ILE A1245     124.882 173.797 179.413  1.00  8.47           H
ATOM  15235 HD12 ILE A1245     125.220 172.263 179.175  1.00  8.47           H
ATOM  15236 HD13 ILE A1245     124.030 172.673 180.144  1.00  8.47           H
ATOM  15237  N   VAL A1246     127.893 169.228 182.720  1.00 10.08           N
ATOM  15238  CA  VAL A1246     128.034 168.001 183.501  1.00 10.08           C
ATOM  15239  C   VAL A1246     129.134 168.163 184.541  1.00 10.08           C
ATOM  15240  O   VAL A1246     129.013 167.692 185.678  1.00 10.08           O
ATOM  15241  CB  VAL A1246     128.303 166.802 182.573  1.00 10.08           C
ATOM  15242  CG1 VAL A1246     128.570 165.545 183.390  1.00 10.08           C
ATOM  15243  CG2 VAL A1246     127.129 166.589 181.630  1.00 10.08           C
ATOM  15244  H   VAL A1246     128.038 169.138 181.877  1.00 10.08           H
ATOM  15245  HA  VAL A1246     127.203 167.832 183.971  1.00 10.08           H
ATOM  15246  HB  VAL A1246     129.090 166.986 182.037  1.00 10.08           H
ATOM  15247 HG11 VAL A1246     128.505 164.773 182.807  1.00 10.08           H
ATOM  15248 HG12 VAL A1246     129.460 165.595 183.771  1.00 10.08           H
ATOM  15249 HG13 VAL A1246     127.908 165.481 184.096  1.00 10.08           H
ATOM  15250 HG21 VAL A1246     127.315 165.825 181.063  1.00 10.08           H
ATOM  15251 HG22 VAL A1246     126.330 166.425 182.154  1.00 10.08           H
ATOM  15252 HG23 VAL A1246     127.010 167.383 181.086  1.00 10.08           H
ATOM  15253  N   GLY A1247     130.225 168.833 184.167  1.00 10.63           N
ATOM  15254  CA  GLY A1247     131.317 169.041 185.097  1.00 10.63           C
ATOM  15255  C   GLY A1247     130.956 169.973 186.233  1.00 10.63           C
ATOM  15256  O   GLY A1247     131.418 169.793 187.358  1.00 10.63           O
ATOM  15257  H   GLY A1247     130.350 169.171 183.387  1.00 10.63           H
ATOM  15258  HA2 GLY A1247     131.596 168.190 185.469  1.00 10.63           H
ATOM  15259  HA3 GLY A1247     132.059 169.429 184.619  1.00 10.63           H
ATOM  15260  N   MET A1248     130.153 170.999 185.954  1.00 10.80           N
ATOM  15261  CA  MET A1248     129.682 171.864 187.029  1.00 10.80           C
ATOM  15262  C   MET A1248     128.869 171.062 188.033  1.00 10.80           C
ATOM  15263  O   MET A1248     129.064 171.180 189.250  1.00 10.80           O
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ATOM  15264  CB  MET A1248     128.850 173.015 186.463  1.00 10.80           C
ATOM  15265  CG  MET A1248     129.646 174.090 185.729  1.00 10.80           C
ATOM  15266  SD  MET A1248     130.719 175.088 186.784  1.00 10.80           S
ATOM  15267  CE  MET A1248     132.247 174.145 186.740  1.00 10.80           C
ATOM  15268  H   MET A1248     129.876 171.213 185.168  1.00 10.80           H
ATOM  15269  HA  MET A1248     130.440 172.240 187.494  1.00 10.80           H
ATOM  15270  HB2 MET A1248     128.206 172.648 185.837  1.00 10.80           H
ATOM  15271  HB3 MET A1248     128.381 173.444 187.195  1.00 10.80           H
ATOM  15272  HG2 MET A1248     130.204 173.664 185.061  1.00 10.80           H
ATOM  15273  HG3 MET A1248     129.021 174.694 185.295  1.00 10.80           H
ATOM  15274  HE1 MET A1248     132.943 174.660 187.175  1.00 10.80           H
ATOM  15275  HE2 MET A1248     132.135 173.302 187.201  1.00 10.80           H
ATOM  15276  HE3 MET A1248     132.485 173.987 185.813  1.00 10.80           H
ATOM  15277  N   PHE A1249     127.964 170.215 187.536  1.00 14.74           N
ATOM  15278  CA  PHE A1249     127.198 169.363 188.443  1.00 14.74           C
ATOM  15279  C   PHE A1249     128.120 168.449 189.247  1.00 14.74           C
ATOM  15280  O   PHE A1249     127.993 168.334 190.476  1.00 14.74           O
ATOM  15281  CB  PHE A1249     126.179 168.541 187.655  1.00 14.74           C
ATOM  15282  CG  PHE A1249     124.865 169.239 187.449  1.00 14.74           C
ATOM  15283  CD1 PHE A1249     123.999 169.436 188.511  1.00 14.74           C
ATOM  15284  CD2 PHE A1249     124.493 169.692 186.194  1.00 14.74           C
ATOM  15285  CE1 PHE A1249     122.788 170.075 188.327  1.00 14.74           C
ATOM  15286  CE2 PHE A1249     123.282 170.331 186.004  1.00 14.74           C
ATOM  15287  CZ  PHE A1249     122.429 170.523 187.073  1.00 14.74           C
ATOM  15288  H   PHE A1249     127.778 170.120 186.702  1.00 14.74           H
ATOM  15289  HA  PHE A1249     126.714 169.924 189.069  1.00 14.74           H
ATOM  15290  HB2 PHE A1249     126.549 168.343 186.780  1.00 14.74           H
ATOM  15291  HB3 PHE A1249     126.005 167.715 188.134  1.00 14.74           H
ATOM  15292  HD1 PHE A1249     124.236 169.137 189.358  1.00 14.74           H
ATOM  15293  HD2 PHE A1249     125.064 169.565 185.471  1.00 14.74           H
ATOM  15294  HE1 PHE A1249     122.215 170.203 189.049  1.00 14.74           H
ATOM  15295  HE2 PHE A1249     123.042 170.633 185.157  1.00 14.74           H
ATOM  15296  HZ  PHE A1249     121.614 170.953 186.947  1.00 14.74           H
ATOM  15297  N   LEU A1250     129.068 167.801 188.568  1.00 17.81           N
ATOM  15298  CA  LEU A1250     129.948 166.854 189.246  1.00 17.81           C
ATOM  15299  C   LEU A1250     130.825 167.551 190.278  1.00 17.81           C
ATOM  15300  O   LEU A1250     131.081 167.001 191.351  1.00 17.81           O
ATOM  15301  CB  LEU A1250     130.813 166.113 188.226  1.00 17.81           C
ATOM  15302  CG  LEU A1250     131.434 164.775 188.647  1.00 17.81           C
ATOM  15303  CD1 LEU A1250     130.456 163.901 189.425  1.00 17.81           C
ATOM  15304  CD2 LEU A1250     131.974 164.030 187.440  1.00 17.81           C
ATOM  15305  H   LEU A1250     129.220 167.891 187.727  1.00 17.81           H
ATOM  15306  HA  LEU A1250     129.396 166.209 189.714  1.00 17.81           H
ATOM  15307  N   ALA A1251     131.316 168.750 189.962  1.00 16.97           N
ATOM  15308  CA  ALA A1251     132.136 169.493 190.910  1.00 16.97           C
ATOM  15309  C   ALA A1251     131.319 169.926 192.117  1.00 16.97           C
ATOM  15310  O   ALA A1251     131.796 169.851 193.256  1.00 16.97           O
ATOM  15311  CB  ALA A1251     132.762 170.706 190.222  1.00 16.97           C
ATOM  15312  H   ALA A1251     131.187 169.150 189.211  1.00 16.97           H
ATOM  15313  HA  ALA A1251     132.855 168.922 191.222  1.00 16.97           H
ATOM  15314  HB1 ALA A1251     133.306 171.188 190.864  1.00 16.97           H
ATOM  15315  HB2 ALA A1251     133.312 170.401 189.484  1.00 16.97           H
ATOM  15316  HB3 ALA A1251     132.054 171.280 189.891  1.00 16.97           H
ATOM  15317  N   ASP A1252     130.083 170.382 191.892  1.00 20.66           N
ATOM  15318  CA  ASP A1252     129.217 170.708 193.018  1.00 20.66           C
ATOM  15319  C   ASP A1252     129.030 169.496 193.918  1.00 20.66           C
ATOM  15320  O   ASP A1252     129.030 169.618 195.149  1.00 20.66           O
ATOM  15321  CB  ASP A1252     127.866 171.214 192.512  1.00 20.66           C
ATOM  15322  CG  ASP A1252     127.016 171.818 193.616  1.00 20.66           C
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ATOM  15323  OD1 ASP A1252     126.889 171.190 194.689  1.00 20.66        O
ATOM  15324  OD2 ASP A1252     126.473 172.924 193.411  1.00 20.66        O
ATOM  15325  H   ASP A1252     129.734 170.506 191.116  1.00 20.66        H
ATOM  15326  HA  ASP A1252     129.628 171.413 193.542  1.00 20.66        H
ATOM  15327  HB2 ASP A1252     128.013 171.894 191.837  1.00 20.66        H
ATOM  15328  HB3 ASP A1252     127.374 170.470 192.130  1.00 20.66        H
ATOM  15329  N   LEU A1253     128.874 168.313 193.321  1.00 24.50        N
ATOM  15330  CA  LEU A1253     128.697 167.108 194.127  1.00 24.50        C
ATOM  15331  C   LEU A1253     129.984 166.725 194.854  1.00 24.50        C
ATOM  15332  O   LEU A1253     129.947 166.325 196.022  1.00 24.50        O
ATOM  15333  CB  LEU A1253     128.213 165.958 193.241  1.00 24.50        C
ATOM  15334  CG  LEU A1253     128.102 164.574 193.891  1.00 24.50        C
ATOM  15335  CD1 LEU A1253     127.006 163.767 193.214  1.00 24.50        C
ATOM  15336  CD2 LEU A1253     129.424 163.814 193.842  1.00 24.50        C
ATOM  15337  H   LEU A1253     128.868 168.184 192.471  1.00 24.50        H
ATOM  15338  HA  LEU A1253     128.015 167.275 194.796  1.00 24.50        H
ATOM  15339  HB2 LEU A1253     127.331 166.188 192.910  1.00 24.50        H
ATOM  15340  HB3 LEU A1253     128.822 165.879 192.490  1.00 24.50        H
ATOM  15341  HG  LEU A1253     127.857 164.685 194.823  1.00 24.50        H
ATOM  15342 HD11 LEU A1253     126.942 162.899 193.643  1.00 24.50        H
ATOM  15343 HD12 LEU A1253     126.164 164.241 193.303  1.00 24.50        H
ATOM  15344 HD13 LEU A1253     127.228 163.658 192.276  1.00 24.50        H
ATOM  15345 HD21 LEU A1253     129.240 162.862 193.860  1.00 24.50        H
ATOM  15346 HD22 LEU A1253     129.895 164.042 193.026  1.00 24.50        H
ATOM  15347 HD23 LEU A1253     129.961 164.059 194.612  1.00 24.50        H
ATOM  15348  N   ILE A1254     131.130 166.837 194.180  1.00 22.27        N
ATOM  15349  CA  ILE A1254     132.383 166.340 194.740  1.00 22.27        C
ATOM  15350  C   ILE A1254     132.877 167.247 195.860  1.00 22.27        C
ATOM  15351  O   ILE A1254     133.372 166.770 196.888  1.00 22.27        O
ATOM  15352  CB  ILE A1254     133.438 166.196 193.627  1.00 22.27        C
ATOM  15353  CG1 ILE A1254     133.099 165.003 192.729  1.00 22.27        C
ATOM  15354  CG2 ILE A1254     134.834 166.045 194.232  1.00 22.27        C
ATOM  15355  CD1 ILE A1254     133.997 164.866 191.515  1.00 22.27        C
ATOM  15356  H   ILE A1254     131.206 167.194 193.402  1.00 22.27        H
ATOM  15357  HA  ILE A1254     132.230 165.460 195.118  1.00 22.27        H
ATOM  15358  HB  ILE A1254     133.424 167.000 193.086  1.00 22.27        H
ATOM  15359 HG12 ILE A1254     133.182 164.188 193.250  1.00 22.27        H
ATOM  15360 HG13 ILE A1254     132.187 165.098 192.414  1.00 22.27        H
ATOM  15361 HG21 ILE A1254     135.443 165.710 193.558  1.00 22.27        H
ATOM  15362 HG22 ILE A1254     135.141 166.911 194.544  1.00 22.27        H
ATOM  15363 HG23 ILE A1254     134.790 165.422 194.974  1.00 22.27        H
ATOM  15364 HD11 ILE A1254     133.567 164.285 190.869  1.00 22.27        H
ATOM  15365 HD12 ILE A1254     134.139 165.744 191.128  1.00 22.27        H
ATOM  15366 HD13 ILE A1254     134.846 164.485 191.789  1.00 22.27        H
ATOM  15367  N   GLU A1255     132.760 168.565 195.681  1.00 25.31        N
ATOM  15368  CA  GLU A1255     133.384 169.498 196.615  1.00 25.31        C
ATOM  15369  C   GLU A1255     132.867 169.292 198.034  1.00 25.31        C
ATOM  15370  O   GLU A1255     133.646 169.275 198.995  1.00 25.31        O
ATOM  15371  CB  GLU A1255     133.137 170.936 196.158  1.00 25.31        C
ATOM  15372  CG  GLU A1255     133.947 171.346 194.938  1.00 25.31        C
ATOM  15373  CD  GLU A1255     133.468 172.649 194.327  1.00 25.31        C
ATOM  15374  OE1 GLU A1255     132.363 173.107 194.686  1.00 25.31        O
ATOM  15375  OE2 GLU A1255     134.199 173.219 193.490  1.00 25.31        O
ATOM  15376  H   GLU A1255     132.331 168.937 195.036  1.00 25.31        H
ATOM  15377  HA  GLU A1255     134.342 169.345 196.620  1.00 25.31        H
ATOM  15378  HB2 GLU A1255     132.197 171.033 195.937  1.00 25.31        H
ATOM  15379  HB3 GLU A1255     133.368 171.538 196.882  1.00 25.31        H
ATOM  15380  HG2 GLU A1255     134.874 171.461 195.199  1.00 25.31        H
ATOM  15381  HG3 GLU A1255     133.877 170.653 194.262  1.00 25.31        H
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ATOM  15382  N   THR A1256     131.552 169.132 198.188  1.00 32.68           N
ATOM  15383  CA  THR A1256     130.980 169.003 199.525  1.00 32.68           C
ATOM  15384  C   THR A1256     131.323 167.657 200.151  1.00 32.68           C
ATOM  15385  O   THR A1256     131.572 167.575 201.360  1.00 32.68           O
ATOM  15386  CB  THR A1256     129.465 169.195 199.469  1.00 32.68           C
ATOM  15387  OG1 THR A1256     128.891 168.238 198.569  1.00 32.68           O
ATOM  15388  CG2 THR A1256     129.122 170.601 199.000  1.00 32.68           C
ATOM  15389  H   THR A1256     130.980 169.096 197.547  1.00 32.68           H
ATOM  15390  HA  THR A1256     131.349 169.699 200.092  1.00 32.68           H
ATOM  15391  HB  THR A1256     129.092 169.068 200.355  1.00 32.68           H
ATOM  15392  HG1 THR A1256     128.059 168.347 198.527  1.00 32.68           H
ATOM  15393 HG21 THR A1256     128.165 170.745 199.053  1.00 32.68           H
ATOM  15394 HG22 THR A1256     129.570 171.255 199.559  1.00 32.68           H
ATOM  15395 HG23 THR A1256     129.410 170.724 198.081  1.00 32.68           H
ATOM  15396  N   TYR A1257     131.342 166.593 199.353  1.00 33.33           N
ATOM  15397  CA  TYR A1257     131.603 165.250 199.856  1.00 33.33           C
ATOM  15398  C   TYR A1257     133.086 164.897 199.872  1.00 33.33           C
ATOM  15399  O   TYR A1257     133.438 163.800 200.318  1.00 33.33           O
ATOM  15400  CB  TYR A1257     130.823 164.225 199.027  1.00 33.33           C
ATOM  15401  CG  TYR A1257     129.323 164.333 199.209  1.00 33.33           C
ATOM  15402  CD1 TYR A1257     128.664 163.578 200.170  1.00 33.33           C
ATOM  15403  CD2 TYR A1257     128.572 165.207 198.436  1.00 33.33           C
ATOM  15404  CE1 TYR A1257     127.295 163.680 200.343  1.00 33.33           C
ATOM  15405  CE2 TYR A1257     127.205 165.316 198.603  1.00 33.33           C
ATOM  15406  CZ  TYR A1257     126.572 164.551 199.557  1.00 33.33           C
ATOM  15407  OH  TYR A1257     125.211 164.660 199.724  1.00 33.33           O
ATOM  15408  H   TYR A1257     131.203 166.624 198.504  1.00 33.33           H
ATOM  15409  HA  TYR A1257     131.279 165.195 200.768  1.00 33.33           H
ATOM  15410  HB2 TYR A1257     131.020 164.363 198.087  1.00 33.33           H
ATOM  15411  HB3 TYR A1257     131.092 163.333 199.294  1.00 33.33           H
ATOM  15412  HD1 TYR A1257     129.149 162.989 200.700  1.00 33.33           H
ATOM  15413  HD2 TYR A1257     128.993 165.724 197.793  1.00 33.33           H
ATOM  15414  HE1 TYR A1257     126.866 163.165 200.987  1.00 33.33           H
ATOM  15415  HE2 TYR A1257     126.716 165.904 198.074  1.00 33.33           H
ATOM  15416  HH  TYR A1257     124.960 164.183 200.368  1.00 33.33           H
ATOM  15417  N   PHE A1258     133.953 165.791 199.402  1.00 32.31           N
ATOM  15418  CA  PHE A1258     135.399 165.689 199.602  1.00 32.31           C
ATOM  15419  C   PHE A1258     135.929 164.303 199.232  1.00 32.31           C
ATOM  15420  O   PHE A1258     136.403 163.540 200.075  1.00 32.31           O
ATOM  15421  CB  PHE A1258     135.768 166.048 201.044  1.00 32.31           C
ATOM  15422  N   VAL A1259     135.833 163.980 197.941  1.00 28.46           N
ATOM  15423  CA  VAL A1259     136.362 162.705 197.459  1.00 28.46           C
ATOM  15424  C   VAL A1259     137.874 162.656 197.652  1.00 28.46           C
ATOM  15425  O   VAL A1259     138.397 161.825 198.403  1.00 28.46           O
ATOM  15426  CB  VAL A1259     135.974 162.481 195.987  1.00 28.46           C
ATOM  15427  N   SER A1260     138.597 163.555 196.981  1.00 19.09           N
ATOM  15428  CA  SER A1260     140.041 163.666 197.151  1.00 19.09           C
ATOM  15429  C   SER A1260     140.562 164.900 196.420  1.00 19.09           C
ATOM  15430  O   SER A1260     140.083 165.214 195.323  1.00 19.09           O
ATOM  15431  CB  SER A1260     140.747 162.410 196.635  1.00 19.09           C
ATOM  15432  OG  SER A1260     142.154 162.531 196.759  1.00 19.09           O
ATOM  15433  HA  SER A1260     140.234 163.749 198.097  1.00 19.09           H
ATOM  15434  HB2 SER A1260     140.452 161.644 197.151  1.00 19.09           H
ATOM  15435  HB3 SER A1260     140.524 162.285 195.699  1.00 19.09           H
ATOM  15436  HG  SER A1260     142.362 162.647 197.565  1.00 19.09           H
ATOM  15437  N   PRO A1261     141.534 165.626 196.985  1.00 14.96           N
ATOM  15438  CA  PRO A1261     142.071 166.793 196.262  1.00 14.96           C
ATOM  15439  C   PRO A1261     142.656 166.448 194.903  1.00 14.96           C
ATOM  15440  O   PRO A1261     142.472 167.208 193.943  1.00 14.96           O
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ATOM  15441  CB  PRO A1261     143.145 167.339 197.214  1.00 14.96           C
ATOM  15442  CG  PRO A1261     142.810 166.799 198.554  1.00 14.96           C
ATOM  15443  CD  PRO A1261     142.066 165.518 198.355  1.00 14.96           C
ATOM  15444  HA  PRO A1261     141.377 167.462 196.148  1.00 14.96           H
ATOM  15445  HB2 PRO A1261     144.018 167.028 196.930  1.00 14.96           H
ATOM  15446  HB3 PRO A1261     143.112 168.308 197.219  1.00 14.96           H
ATOM  15447  HG2 PRO A1261     143.630 166.637 199.047  1.00 14.96           H
ATOM  15448  HG3 PRO A1261     142.255 167.439 199.026  1.00 14.96           H
ATOM  15449  HD2 PRO A1261     142.670 164.762 198.425  1.00 14.96           H
ATOM  15450  HD3 PRO A1261     141.340 165.452 198.996  1.00 14.96           H
ATOM  15451  N   THR A1262     143.357 165.318 194.791  1.00 10.97           N
ATOM  15452  CA  THR A1262     143.983 164.964 193.520  1.00 10.97           C
ATOM  15453  C   THR A1262     142.936 164.634 192.464  1.00 10.97           C
ATOM  15454  O   THR A1262     143.101 164.982 191.289  1.00 10.97           O
ATOM  15455  CB  THR A1262     144.938 163.786 193.710  1.00 10.97           C
ATOM  15456  OG1 THR A1262     145.852 164.076 194.775  1.00 10.97           O
ATOM  15457  CG2 THR A1262     145.723 163.519 192.431  1.00 10.97           C
ATOM  15458  H   THR A1262     143.483 164.749 195.424  1.00 10.97           H
ATOM  15459  HA  THR A1262     144.500 165.721 193.202  1.00 10.97           H
ATOM  15460  HB  THR A1262     144.428 162.991 193.928  1.00 10.97           H
ATOM  15461  HG1 THR A1262     146.413 163.456 194.846  1.00 10.97           H
ATOM  15462 HG21 THR A1262     146.420 162.868 192.602  1.00 10.97           H
ATOM  15463 HG22 THR A1262     145.132 163.175 191.743  1.00 10.97           H
ATOM  15464 HG23 THR A1262     146.131 164.341 192.116  1.00 10.97           H
ATOM  15465  N   LEU A1263     141.857 163.958 192.860  1.00 11.85           N
ATOM  15466  CA  LEU A1263     140.784 163.671 191.914  1.00 11.85           C
ATOM  15467  C   LEU A1263     140.143 164.959 191.415  1.00 11.85           C
ATOM  15468  O   LEU A1263     139.828 165.086 190.225  1.00 11.85           O
ATOM  15469  CB  LEU A1263     139.743 162.762 192.570  1.00 11.85           C
ATOM  15470  CG  LEU A1263     138.428 162.548 191.817  1.00 11.85           C
ATOM  15471  CD1 LEU A1263     138.667 161.748 190.548  1.00 11.85           C
ATOM  15472  CD2 LEU A1263     137.419 161.847 192.709  1.00 11.85           C
ATOM  15473  H   LEU A1263     141.725 163.660 193.656  1.00 11.85           H
ATOM  15474  HA  LEU A1263     141.153 163.202 191.149  1.00 11.85           H
ATOM  15475  HB2 LEU A1263     140.144 161.888 192.697  1.00 11.85           H
ATOM  15476  HB3 LEU A1263     139.518 163.138 193.435  1.00 11.85           H
ATOM  15477  HG  LEU A1263     138.053 163.406 191.566  1.00 11.85           H
ATOM  15478 HD11 LEU A1263     137.822 161.624 190.089  1.00 11.85           H
ATOM  15479 HD12 LEU A1263     139.284 162.236 189.980  1.00 11.85           H
ATOM  15480 HD13 LEU A1263     139.045 160.887 190.785  1.00 11.85           H
ATOM  15481 HD21 LEU A1263     136.594 161.721 192.215  1.00 11.85           H
ATOM  15482 HD22 LEU A1263     137.779 160.988 192.978  1.00 11.85           H
ATOM  15483 HD23 LEU A1263     137.255 162.397 193.492  1.00 11.85           H
ATOM  15484  N   PHE A1264     139.935 165.925 192.313  1.00  9.59           N
ATOM  15485  CA  PHE A1264     139.396 167.216 191.898  1.00  9.59           C
ATOM  15486  C   PHE A1264     140.348 167.915 190.936  1.00  9.59           C
ATOM  15487  O   PHE A1264     139.920 168.474 189.919  1.00  9.59           O
ATOM  15488  CB  PHE A1264     139.132 168.086 193.127  1.00  9.59           C
ATOM  15489  CG  PHE A1264     138.433 169.380 192.821  1.00  9.59           C
ATOM  15490  CD1 PHE A1264     137.241 169.391 192.115  1.00  9.59           C
ATOM  15491  CD2 PHE A1264     138.965 170.586 193.246  1.00  9.59           C
ATOM  15492  CE1 PHE A1264     136.595 170.581 191.837  1.00  9.59           C
ATOM  15493  CE2 PHE A1264     138.324 171.779 192.969  1.00  9.59           C
ATOM  15494  CZ  PHE A1264     137.138 171.776 192.264  1.00  9.59           C
ATOM  15495  H   PHE A1264     140.095 165.857 193.155  1.00  9.59           H
ATOM  15496  HA  PHE A1264     138.554 167.072 191.438  1.00  9.59           H
ATOM  15497  HB2 PHE A1264     138.576 167.589 193.748  1.00  9.59           H
ATOM  15498  HB3 PHE A1264     139.980 168.300 193.546  1.00  9.59           H
ATOM  15499  HD1 PHE A1264     136.871 168.589 191.825  1.00  9.59           H
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ATOM  15500  HD2 PHE A1264     139.764 170.593 193.722  1.00  9.59           H
ATOM  15501  HE1 PHE A1264     135.797 170.577 191.361  1.00  9.59           H
ATOM  15502  HE2 PHE A1264     138.692 172.582 193.259  1.00  9.59           H
ATOM  15503  HZ  PHE A1264     136.705 172.578 192.077  1.00  9.59           H
ATOM  15504  N   ARG A1265     141.650 167.876 191.231  1.00  7.07           N
ATOM  15505  CA  ARG A1265     142.630 168.475 190.332  1.00  7.07           C
ATOM  15506  C   ARG A1265     142.580 167.824 188.956  1.00  7.07           C
ATOM  15507  O   ARG A1265     142.653 168.511 187.931  1.00  7.07           O
ATOM  15508  CB  ARG A1265     144.031 168.344 190.929  1.00  7.07           C
ATOM  15509  CG  ARG A1265     144.303 169.258 192.112  1.00  7.07           C
ATOM  15510  CD  ARG A1265     145.646 168.935 192.754  1.00  7.07           C
ATOM  15511  NE  ARG A1265     146.603 170.030 192.630  1.00  7.07           N
ATOM  15512  CZ  ARG A1265     147.853 169.988 193.084  1.00  7.07           C
ATOM  15513  NH1 ARG A1265     148.308 168.904 193.697  1.00  7.07           N
ATOM  15514  NH2 ARG A1265     148.649 171.033 192.922  1.00  7.07           N
ATOM  15515  H   ARG A1265     141.984 167.514 191.936  1.00  7.07           H
ATOM  15516  HA  ARG A1265     142.432 169.419 190.228  1.00  7.07           H
ATOM  15517  HB2 ARG A1265     144.155 167.430 191.228  1.00  7.07           H
ATOM  15518  HB3 ARG A1265     144.682 168.553 190.240  1.00  7.07           H
ATOM  15519  HG2 ARG A1265     144.323 170.179 191.809  1.00  7.07           H
ATOM  15520  HG3 ARG A1265     143.609 169.137 192.779  1.00  7.07           H
ATOM  15521  HD2 ARG A1265     145.512 168.759 193.698  1.00  7.07           H
ATOM  15522  HD3 ARG A1265     146.026 168.154 192.321  1.00  7.07           H
ATOM  15523  HE  ARG A1265     146.325 170.769 192.290  1.00  7.07           H
ATOM  15524 HH11 ARG A1265     147.797 168.221 193.806  1.00  7.07           H
ATOM  15525 HH12 ARG A1265     149.117 168.885 193.989  1.00  7.07           H
ATOM  15526 HH21 ARG A1265     148.356 171.736 192.524  1.00  7.07           H
ATOM  15527 HH22 ARG A1265     149.458 171.009 193.215  1.00  7.07           H
ATOM  15528  N   VAL A1266     142.459 166.497 188.916  1.00  7.00           N
ATOM  15529  CA  VAL A1266     142.464 165.784 187.643  1.00  7.00           C
ATOM  15530  C   VAL A1266     141.209 166.110 186.842  1.00  7.00           C
ATOM  15531  O   VAL A1266     141.279 166.408 185.644  1.00  7.00           O
ATOM  15532  CB  VAL A1266     142.602 164.270 187.880  1.00  7.00           C
ATOM  15533  CG1 VAL A1266     142.487 163.512 186.565  1.00  7.00           C
ATOM  15534  CG2 VAL A1266     143.922 163.963 188.568  1.00  7.00           C
ATOM  15535  H   VAL A1266     142.375 165.992 189.607  1.00  7.00           H
ATOM  15536  HA  VAL A1266     143.231 166.074 187.124  1.00  7.00           H
ATOM  15537  N   ILE A1267     140.040 166.058 187.488  1.00  8.29           N
ATOM  15538  CA  ILE A1267     138.799 166.319 186.768  1.00  8.29           C
ATOM  15539  C   ILE A1267     138.662 167.790 186.400  1.00  8.29           C
ATOM  15540  O   ILE A1267     137.869 168.128 185.514  1.00  8.29           O
ATOM  15541  CB  ILE A1267     137.578 165.848 187.583  1.00  8.29           C
ATOM  15542  CG1 ILE A1267     137.429 166.673 188.862  1.00  8.29           C
ATOM  15543  CG2 ILE A1267     137.691 164.362 187.902  1.00  8.29           C
ATOM  15544  CD1 ILE A1267     136.359 167.740 188.775  1.00  8.29           C
ATOM  15545  H   ILE A1267     139.943 165.878 188.323  1.00  8.29           H
ATOM  15546  HA  ILE A1267     138.810 165.811 185.942  1.00  8.29           H
ATOM  15547  HB  ILE A1267     136.784 165.982 187.042  1.00  8.29           H
ATOM  15548 HG12 ILE A1267     137.196 166.079 189.592  1.00  8.29           H
ATOM  15549 HG13 ILE A1267     138.270 167.111 189.051  1.00  8.29           H
ATOM  15550 HG21 ILE A1267     136.908 164.087 188.402  1.00  8.29           H
ATOM  15551 HG22 ILE A1267     137.743 163.866 187.070  1.00  8.29           H
ATOM  15552 HG23 ILE A1267     138.491 164.209 188.428  1.00  8.29           H
ATOM  15553 HD11 ILE A1267     136.367 168.261 189.594  1.00  8.29           H
ATOM  15554 HD12 ILE A1267     136.544 168.315 188.016  1.00  8.29           H
ATOM  15555 HD13 ILE A1267     135.496 167.313 188.664  1.00  8.29           H
ATOM  15556  N   ARG A1268     139.412 168.681 187.053  1.00  6.16           N
ATOM  15557  CA  ARG A1268     139.418 170.081 186.649  1.00  6.16           C
ATOM  15558  C   ARG A1268     140.088 170.302 185.299  1.00  6.16           C
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ATOM  15559  O   ARG A1268     139.953 171.392 184.733  1.00  6.16           O
ATOM  15560  CB  ARG A1268     140.121 170.928 187.710  1.00  6.16           C
ATOM  15561  CG  ARG A1268     139.188 171.525 188.751  1.00  6.16           C
ATOM  15562  CD  ARG A1268     139.933 172.472 189.680  1.00  6.16           C
ATOM  15563  NE  ARG A1268     140.280 173.728 189.018  1.00  6.16           N
ATOM  15564  CZ  ARG A1268     141.330 174.484 189.330  1.00  6.16           C
ATOM  15565  NH1 ARG A1268     142.157 174.126 190.304  1.00  6.16           N
ATOM  15566  NH2 ARG A1268     141.554 175.609 188.664  1.00  6.16           N
ATOM  15567  H   ARG A1268     139.918 168.499 187.724  1.00  6.16           H
ATOM  15568  HA  ARG A1268     138.501 170.390 186.580  1.00  6.16           H
ATOM  15569  HB2 ARG A1268     140.767 170.374 188.176  1.00  6.16           H
ATOM  15570  HB3 ARG A1268     140.578 171.662 187.270  1.00  6.16           H
ATOM  15571  HG2 ARG A1268     138.487 172.025 188.305  1.00  6.16           H
ATOM  15572  HG3 ARG A1268     138.806 170.812 189.286  1.00  6.16           H
ATOM  15573  HD2 ARG A1268     139.372 172.677 190.444  1.00  6.16           H
ATOM  15574  HD3 ARG A1268     140.751 172.041 189.971  1.00  6.16           H
ATOM  15575  HE  ARG A1268     139.755 174.011 188.397  1.00  6.16           H
ATOM  15576 HH11 ARG A1268     142.023 173.401 190.744  1.00  6.16           H
ATOM  15577 HH12 ARG A1268     142.831 174.624 190.496  1.00  6.16           H
ATOM  15578 HH21 ARG A1268     141.022 175.847 188.031  1.00  6.16           H
ATOM  15579 HH22 ARG A1268     142.231 176.099 188.863  1.00  6.16           H
ATOM  15580  N   LEU A1269     140.801 169.304 184.770  1.00  7.10           N
ATOM  15581  CA  LEU A1269     141.495 169.477 183.499  1.00  7.10           C
ATOM  15582  C   LEU A1269     140.538 169.753 182.348  1.00  7.10           C
ATOM  15583  O   LEU A1269     140.958 170.305 181.326  1.00  7.10           O
ATOM  15584  CB  LEU A1269     142.335 168.237 183.187  1.00  7.10           C
ATOM  15585  CG  LEU A1269     143.619 168.075 184.005  1.00  7.10           C
ATOM  15586  CD1 LEU A1269     144.122 166.641 183.934  1.00  7.10           C
ATOM  15587  CD2 LEU A1269     144.691 169.043 183.524  1.00  7.10           C
ATOM  15588  H   LEU A1269     140.896 168.526 185.125  1.00  7.10           H
ATOM  15589  HA  LEU A1269     142.096 170.235 183.573  1.00  7.10           H
ATOM  15590  HB2 LEU A1269     141.790 167.451 183.346  1.00  7.10           H
ATOM  15591  HB3 LEU A1269     142.590 168.269 182.252  1.00  7.10           H
ATOM  15592  HG  LEU A1269     143.428 168.279 184.934  1.00  7.10           H
ATOM  15593 HD11 LEU A1269     143.708 166.128 184.646  1.00  7.10           H
ATOM  15594 HD12 LEU A1269     143.884 166.265 183.073  1.00  7.10           H
ATOM  15595 HD13 LEU A1269     145.086 166.639 184.044  1.00  7.10           H
ATOM  15596 HD21 LEU A1269     145.459 168.979 184.113  1.00  7.10           H
ATOM  15597 HD22 LEU A1269     144.947 168.805 182.619  1.00  7.10           H
ATOM  15598 HD23 LEU A1269     144.335 169.945 183.543  1.00  7.10           H
ATOM  15599  N   ALA A1270     139.263 169.381 182.486  1.00  4.99           N
ATOM  15600  CA  ALA A1270     138.297 169.642 181.426  1.00  4.99           C
ATOM  15601  C   ALA A1270     138.042 171.131 181.231  1.00  4.99           C
ATOM  15602  O   ALA A1270     137.486 171.523 180.199  1.00  4.99           O
ATOM  15603  CB  ALA A1270     136.984 168.923 181.729  1.00  4.99           C
ATOM  15604  H   ALA A1270     138.939 168.980 183.174  1.00  4.99           H
ATOM  15605  HA  ALA A1270     138.644 169.289 180.592  1.00  4.99           H
ATOM  15606  HB1 ALA A1270     136.313 169.202 181.087  1.00  4.99           H
ATOM  15607  HB2 ALA A1270     137.126 167.965 181.668  1.00  4.99           H
ATOM  15608  HB3 ALA A1270     136.706 169.160 182.625  1.00  4.99           H
ATOM  15609  N   ARG A1271     138.430 171.970 182.196  1.00  4.81           N
ATOM  15610  CA  ARG A1271     138.264 173.410 182.041  1.00  4.81           C
ATOM  15611  C   ARG A1271     139.013 173.945 180.828  1.00  4.81           C
ATOM  15612  O   ARG A1271     138.627 174.985 180.283  1.00  4.81           O
ATOM  15613  CB  ARG A1271     138.739 174.131 183.306  1.00  4.81           C
ATOM  15614  CG  ARG A1271     140.254 174.255 183.425  1.00  4.81           C
ATOM  15615  CD  ARG A1271     140.669 174.878 184.747  1.00  4.81           C
ATOM  15616  NE  ARG A1271     142.125 174.931 184.881  1.00  4.81           N
ATOM  15617  CZ  ARG A1271     142.818 175.982 185.312  1.00  4.81           C
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ATOM  15618  NH1 ARG A1271     142.208 177.105 185.673  1.00  4.81           N
ATOM  15619  NH2 ARG A1271     144.140 175.908 185.386  1.00  4.81           N
ATOM  15620  H   ARG A1271     138.787 171.730 182.941  1.00  4.81           H
ATOM  15621  HA  ARG A1271     137.322 173.607 181.921  1.00  4.81           H
ATOM  15622  HB2 ARG A1271     138.369 175.028 183.310  1.00  4.81           H
ATOM  15623  HB3 ARG A1271     138.420 173.643 184.081  1.00  4.81           H
ATOM  15624  HG2 ARG A1271     140.652 173.372 183.367  1.00  4.81           H
ATOM  15625  HG3 ARG A1271     140.591 174.822 182.715  1.00  4.81           H
ATOM  15626  HD2 ARG A1271     140.309 175.776 184.790  1.00  4.81           H
ATOM  15627  HD3 ARG A1271     140.317 174.343 185.476  1.00  4.81           H
ATOM  15628  HE  ARG A1271     142.568 174.227 184.661  1.00  4.81           H
ATOM  15629 HH11 ARG A1271     141.354 177.173 185.632  1.00  4.81           H
ATOM  15630 HH12 ARG A1271     142.675 177.773 185.950  1.00  4.81           H
ATOM  15631 HH21 ARG A1271     144.543 175.184 185.156  1.00  4.81           H
ATOM  15632 HH22 ARG A1271     144.594 176.583 185.666  1.00  4.81           H
ATOM  15633  N   ILE A1272     140.071 173.258 180.393  1.00  4.75           N
ATOM  15634  CA  ILE A1272     140.836 173.705 179.236  1.00  4.75           C
ATOM  15635  C   ILE A1272     140.004 173.665 177.961  1.00  4.75           C
ATOM  15636  O   ILE A1272     140.358 174.321 176.974  1.00  4.75           O
ATOM  15637  CB  ILE A1272     142.107 172.846 179.077  1.00  4.75           C
ATOM  15638  CG1 ILE A1272     142.950 172.879 180.357  1.00  4.75           C
ATOM  15639  CG2 ILE A1272     142.932 173.319 177.889  1.00  4.75           C
ATOM  15640  CD1 ILE A1272     143.417 174.264 180.765  1.00  4.75           C
ATOM  15641  H   ILE A1272     140.361 172.531 180.750  1.00  4.75           H
ATOM  15642  HA  ILE A1272     141.110 174.624 179.377  1.00  4.75           H
ATOM  15643  HB  ILE A1272     141.836 171.930 178.916  1.00  4.75           H
ATOM  15644 HG12 ILE A1272     142.427 172.516 181.089  1.00  4.75           H
ATOM  15645 HG13 ILE A1272     143.740 172.332 180.221  1.00  4.75           H
ATOM  15646 HG21 ILE A1272     143.818 172.929 177.949  1.00  4.75           H
ATOM  15647 HG22 ILE A1272     142.501 173.032 177.068  1.00  4.75           H
ATOM  15648 HG23 ILE A1272     142.995 174.286 177.912  1.00  4.75           H
ATOM  15649 HD11 ILE A1272     144.010 174.182 181.529  1.00  4.75           H
ATOM  15650 HD12 ILE A1272     143.891 174.672 180.024  1.00  4.75           H
ATOM  15651 HD13 ILE A1272     142.647 174.803 181.003  1.00  4.75           H
ATOM  15652  N   GLY A1273     138.902 172.913 177.954  1.00  5.01           N
ATOM  15653  CA  GLY A1273     138.130 172.756 176.732  1.00  5.01           C
ATOM  15654  C   GLY A1273     137.619 174.068 176.171  1.00  5.01           C
ATOM  15655  O   GLY A1273     137.660 174.293 174.959  1.00  5.01           O
ATOM  15656  H   GLY A1273     138.589 172.489 178.634  1.00  5.01           H
ATOM  15657  HA2 GLY A1273     138.681 172.330 176.057  1.00  5.01           H
ATOM  15658  HA3 GLY A1273     137.367 172.183 176.908  1.00  5.01           H
ATOM  15659  N   ARG A1274     137.133 174.957 177.040  1.00  5.16           N
ATOM  15660  CA  ARG A1274     136.546 176.204 176.564  1.00  5.16           C
ATOM  15661  C   ARG A1274     137.592 177.252 176.206  1.00  5.16           C
ATOM  15662  O   ARG A1274     137.235 178.295 175.648  1.00  5.16           O
ATOM  15663  CB  ARG A1274     135.577 176.770 177.608  1.00  5.16           C
ATOM  15664  CG  ARG A1274     136.194 177.120 178.952  1.00  5.16           C
ATOM  15665  CD  ARG A1274     135.114 177.567 179.928  1.00  5.16           C
ATOM  15666  NE  ARG A1274     135.652 177.939 181.233  1.00  5.16           N
ATOM  15667  CZ  ARG A1274     135.921 177.077 182.210  1.00  5.16           C
ATOM  15668  NH1 ARG A1274     135.701 175.779 182.043  1.00  5.16           N
ATOM  15669  NH2 ARG A1274     136.408 177.516 183.362  1.00  5.16           N
ATOM  15670  H   ARG A1274     137.131 174.861 177.894  1.00  5.16           H
ATOM  15671  HA  ARG A1274     136.034 176.018 175.762  1.00  5.16           H
ATOM  15672  HB2 ARG A1274     135.178 177.579 177.251  1.00  5.16           H
ATOM  15673  HB3 ARG A1274     134.883 176.111 177.770  1.00  5.16           H
ATOM  15674  HG2 ARG A1274     136.636 176.339 179.320  1.00  5.16           H
ATOM  15675  HG3 ARG A1274     136.826 177.847 178.839  1.00  5.16           H
ATOM  15676  HD2 ARG A1274     134.660 178.343 179.561  1.00  5.16           H
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ATOM  15677  HD3 ARG A1274     134.480 176.844 180.054  1.00  5.16           H
ATOM  15678  HE  ARG A1274     135.726 178.777 181.410  1.00  5.16           H
ATOM  15679 HH11 ARG A1274     135.385 175.483 181.301  1.00  5.16           H
ATOM  15680 HH12 ARG A1274     135.877 175.230 182.681  1.00  5.16           H
ATOM  15681 HH21 ARG A1274     136.551 178.356 183.474  1.00  5.16           H
ATOM  15682 HH22 ARG A1274     136.582 176.961 183.995  1.00  5.16           H
ATOM  15683  N   ILE A1275     138.870 177.002 176.508  1.00  4.40           N
ATOM  15684  CA  ILE A1275     139.939 177.906 176.092  1.00  4.40           C
ATOM  15685  C   ILE A1275     140.562 177.495 174.766  1.00  4.40           C
ATOM  15686  O   ILE A1275     141.210 178.327 174.112  1.00  4.40           O
ATOM  15687  CB  ILE A1275     141.038 177.982 177.172  1.00  4.40           C
ATOM  15688  CG1 ILE A1275     140.453 178.443 178.512  1.00  4.40           C
ATOM  15689  CG2 ILE A1275     142.155 178.921 176.740  1.00  4.40           C
ATOM  15690  CD1 ILE A1275     139.865 179.845 178.494  1.00  4.40           C
ATOM  15691  H   ILE A1275     139.140 176.317 176.952  1.00  4.40           H
ATOM  15692  HA  ILE A1275     139.572 178.795 175.975  1.00  4.40           H
ATOM  15693  HB  ILE A1275     141.413 177.095 177.291  1.00  4.40           H
ATOM  15694 HG12 ILE A1275     139.748 177.831 178.773  1.00  4.40           H
ATOM  15695 HG13 ILE A1275     141.158 178.430 179.178  1.00  4.40           H
ATOM  15696 HG21 ILE A1275     142.736 179.080 177.498  1.00  4.40           H
ATOM  15697 HG22 ILE A1275     142.662 178.511 176.023  1.00  4.40           H
ATOM  15698 HG23 ILE A1275     141.766 179.757 176.439  1.00  4.40           H
ATOM  15699 HD11 ILE A1275     139.438 180.016 179.348  1.00  4.40           H
ATOM  15700 HD12 ILE A1275     140.579 180.485 178.350  1.00  4.40           H
ATOM  15701 HD13 ILE A1275     139.209 179.913 177.784  1.00  4.40           H
ATOM  15702  N   LEU A1276     140.377 176.245 174.338  1.00  4.77           N
ATOM  15703  CA  LEU A1276     140.971 175.772 173.095  1.00  4.77           C
ATOM  15704  C   LEU A1276     140.300 176.363 171.861  1.00  4.77           C
ATOM  15705  O   LEU A1276     140.857 176.264 170.763  1.00  4.77           O
ATOM  15706  CB  LEU A1276     140.902 174.244 173.035  1.00  4.77           C
ATOM  15707  CG  LEU A1276     141.833 173.491 173.992  1.00  4.77           C
ATOM  15708  CD1 LEU A1276     141.512 172.004 173.995  1.00  4.77           C
ATOM  15709  CD2 LEU A1276     143.293 173.718 173.627  1.00  4.77           C
ATOM  15710  H   LEU A1276     139.911 175.653 174.753  1.00  4.77           H
ATOM  15711  HA  LEU A1276     141.904 176.032 173.076  1.00  4.77           H
ATOM  15712  HB2 LEU A1276     139.994 173.971 173.241  1.00  4.77           H
ATOM  15713  HB3 LEU A1276     141.127 173.963 172.134  1.00  4.77           H
ATOM  15714  HG  LEU A1276     141.695 173.826 174.892  1.00  4.77           H
ATOM  15715 HD11 LEU A1276     142.112 171.554 174.610  1.00  4.77           H
ATOM  15716 HD12 LEU A1276     140.593 171.880 174.279  1.00  4.77           H
ATOM  15717 HD13 LEU A1276     141.632 171.653 173.099  1.00  4.77           H
ATOM  15718 HD21 LEU A1276     143.847 173.143 174.177  1.00  4.77           H
ATOM  15719 HD22 LEU A1276     143.420 173.503 172.690  1.00  4.77           H
ATOM  15720 HD23 LEU A1276     143.519 174.647 173.788  1.00  4.77           H
ATOM  15721  N   ARG A1277     139.122 176.970 172.016  1.00  7.12           N
ATOM  15722  CA  ARG A1277     138.421 177.576 170.890  1.00  7.12           C
ATOM  15723  C   ARG A1277     139.115 178.826 170.363  1.00  7.12           C
ATOM  15724  O   ARG A1277     138.751 179.304 169.283  1.00  7.12           O
ATOM  15725  CB  ARG A1277     136.988 177.925 171.299  1.00  7.12           C
ATOM  15726  CG  ARG A1277     136.221 176.771 171.925  1.00  7.12           C
ATOM  15727  CD  ARG A1277     134.820 177.192 172.336  1.00  7.12           C
ATOM  15728  NE  ARG A1277     134.054 177.728 171.213  1.00  7.12           N
ATOM  15729  CZ  ARG A1277     133.116 178.666 171.314  1.00  7.12           C
ATOM  15730  NH1 ARG A1277     132.480 179.081 170.227  1.00  7.12           N
ATOM  15731  NH2 ARG A1277     132.804 179.189 172.494  1.00  7.12           N
ATOM  15732  H   ARG A1277     138.710 177.044 172.766  1.00  7.12           H
ATOM  15733  HA  ARG A1277     138.376 176.933 170.166  1.00  7.12           H
ATOM  15734  HB2 ARG A1277     137.017 178.647 171.947  1.00  7.12           H
ATOM  15735  HB3 ARG A1277     136.502 178.212 170.510  1.00  7.12           H
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ATOM  15736  HG2 ARG A1277     136.144 176.051 171.280  1.00  7.12           H
ATOM  15737  HG3 ARG A1277     136.688 176.464 172.718  1.00  7.12           H
ATOM  15738  HD2 ARG A1277     134.346 176.423 172.688  1.00  7.12           H
ATOM  15739  HD3 ARG A1277     134.894 177.879 173.016  1.00  7.12           H
ATOM  15740  HE  ARG A1277     134.213 177.405 170.432  1.00  7.12           H
ATOM  15741 HH11 ARG A1277     132.677 178.746 169.460  1.00  7.12           H
ATOM  15742 HH12 ARG A1277     131.872 179.686 170.289  1.00  7.12           H
ATOM  15743 HH21 ARG A1277     133.207 178.929 173.207  1.00  7.12           H
ATOM  15744 HH22 ARG A1277     132.194 179.794 172.545  1.00  7.12           H
ATOM  15745  N   LEU A1278     140.095 179.363 171.092  1.00  6.90           N
ATOM  15746  CA  LEU A1278     140.737 180.607 170.681  1.00  6.90           C
ATOM  15747  C   LEU A1278     141.469 180.477 169.352  1.00  6.90           C
ATOM  15748  O   LEU A1278     141.663 181.485 168.664  1.00  6.90           O
ATOM  15749  CB  LEU A1278     141.711 181.069 171.766  1.00  6.90           C
ATOM  15750  CG  LEU A1278     142.255 182.491 171.625  1.00  6.90           C
ATOM  15751  CD1 LEU A1278     141.148 183.523 171.779  1.00  6.90           C
ATOM  15752  CD2 LEU A1278     143.359 182.733 172.640  1.00  6.90           C
ATOM  15753  H   LEU A1278     140.404 179.029 171.821  1.00  6.90           H
ATOM  15754  HA  LEU A1278     140.055 181.288 170.579  1.00  6.90           H
ATOM  15755  HB2 LEU A1278     141.259 181.016 172.623  1.00  6.90           H
ATOM  15756  HB3 LEU A1278     142.472 180.467 171.767  1.00  6.90           H
ATOM  15757  HG  LEU A1278     142.638 182.595 170.740  1.00  6.90           H
ATOM  15758 HD11 LEU A1278     141.540 184.410 171.750  1.00  6.90           H
ATOM  15759 HD12 LEU A1278     140.514 183.421 171.052  1.00  6.90           H
ATOM  15760 HD13 LEU A1278     140.703 183.385 172.630  1.00  6.90           H
ATOM  15761 HD21 LEU A1278     143.745 183.608 172.483  1.00  6.90           H
ATOM  15762 HD22 LEU A1278     142.981 182.692 173.532  1.00  6.90           H
ATOM  15763 HD23 LEU A1278     144.038 182.048 172.536  1.00  6.90           H
ATOM  15764  N   VAL A1279     141.878 179.265 168.971  1.00  7.19           N
ATOM  15765  CA  VAL A1279     142.590 179.087 167.711  1.00  7.19           C
ATOM  15766  C   VAL A1279     141.667 179.208 166.505  1.00  7.19           C
ATOM  15767  O   VAL A1279     142.153 179.302 165.371  1.00  7.19           O
ATOM  15768  CB  VAL A1279     143.309 177.726 167.682  1.00  7.19           C
ATOM  15769  CG1 VAL A1279     144.203 177.572 168.905  1.00  7.19           C
ATOM  15770  CG2 VAL A1279     142.300 176.589 167.605  1.00  7.19           C
ATOM  15771  H   VAL A1279     141.757 178.542 169.420  1.00  7.19           H
ATOM  15772  HA  VAL A1279     143.266 179.779 167.634  1.00  7.19           H
ATOM  15773  HB  VAL A1279     143.870 177.682 166.892  1.00  7.19           H
ATOM  15774 HG11 VAL A1279     144.725 176.761 168.813  1.00  7.19           H
ATOM  15775 HG12 VAL A1279     144.792 178.341 168.962  1.00  7.19           H
ATOM  15776 HG13 VAL A1279     143.649 177.521 169.699  1.00  7.19           H
ATOM  15777 HG21 VAL A1279     142.745 175.759 167.839  1.00  7.19           H
ATOM  15778 HG22 VAL A1279     141.578 176.763 168.229  1.00  7.19           H
ATOM  15779 HG23 VAL A1279     141.951 176.534 166.702  1.00  7.19           H
ATOM  15780  N   LYS A1280     140.353 179.204 166.715  1.00 11.33           N
ATOM  15781  CA  LYS A1280     139.415 179.277 165.602  1.00 11.33           C
ATOM  15782  C   LYS A1280     139.597 180.576 164.825  1.00 11.33           C
ATOM  15783  O   LYS A1280     139.646 181.663 165.408  1.00 11.33           O
ATOM  15784  CB  LYS A1280     137.982 179.169 166.122  1.00 11.33           C
ATOM  15785  CG  LYS A1280     136.987 178.658 165.093  1.00 11.33           C
ATOM  15786  CD  LYS A1280     135.677 179.434 165.129  1.00 11.33           C
ATOM  15787  CE  LYS A1280     134.487 178.523 164.881  1.00 11.33           C
ATOM  15788  NZ  LYS A1280     133.186 179.220 165.078  1.00 11.33           N
ATOM  15789  H   LYS A1280     139.978 179.160 167.488  1.00 11.33           H
ATOM  15790  HA  LYS A1280     139.577 178.536 164.997  1.00 11.33           H
ATOM  15791  HB2 LYS A1280     137.969 178.557 166.874  1.00 11.33           H
ATOM  15792  HB3 LYS A1280     137.693 180.049 166.409  1.00 11.33           H
ATOM  15793  HG2 LYS A1280     137.370 178.752 164.207  1.00 11.33           H
ATOM  15794  HG3 LYS A1280     136.792 177.727 165.275  1.00 11.33           H
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ATOM  15795  HD2 LYS A1280     135.564 179.843 166.002  1.00 11.33        H
ATOM  15796  HD3 LYS A1280     135.688 180.115 164.439  1.00 11.33        H
ATOM  15797  HE2 LYS A1280     134.520 178.191 163.970  1.00 11.33        H
ATOM  15798  HE3 LYS A1280     134.525 177.784 165.507  1.00 11.33        H
ATOM  15799  HZ1 LYS A1280     132.513 178.657 164.927  1.00 11.33        H
ATOM  15800  HZ2 LYS A1280     133.128 179.523 165.912  1.00 11.33        H
ATOM  15801  HZ3 LYS A1280     133.119 179.907 164.515  1.00 11.33        H
ATOM  15802  N   GLY A1281     139.695 180.457 163.501  1.00 12.86        N
ATOM  15803  CA  GLY A1281     139.755 181.592 162.609  1.00 12.86        C
ATOM  15804  C   GLY A1281     141.153 182.010 162.201  1.00 12.86        C
ATOM  15805  O   GLY A1281     141.307 182.680 161.173  1.00 12.86        O
ATOM  15806  H   GLY A1281     139.729 179.701 163.093  1.00 12.86        H
ATOM  15807  HA2 GLY A1281     139.258 181.384 161.803  1.00 12.86        H
ATOM  15808  HA3 GLY A1281     139.328 182.351 163.036  1.00 12.86        H
ATOM  15809  N   ALA A1282     142.172 181.635 162.969  1.00 11.28        N
ATOM  15810  CA  ALA A1282     143.540 182.006 162.632  1.00 11.28        C
ATOM  15811  C   ALA A1282     143.982 181.290 161.361  1.00 11.28        C
ATOM  15812  O   ALA A1282     143.726 180.094 161.190  1.00 11.28        O
ATOM  15813  CB  ALA A1282     144.477 181.669 163.789  1.00 11.28        C
ATOM  15814  H   ALA A1282     142.098 181.168 163.688  1.00 11.28        H
ATOM  15815  HA  ALA A1282     143.583 182.962 162.474  1.00 11.28        H
ATOM  15816  HB1 ALA A1282     145.391 181.853 163.520  1.00 11.28        H
ATOM  15817  HB2 ALA A1282     144.240 182.213 164.556  1.00 11.28        H
ATOM  15818  HB3 ALA A1282     144.378 180.729 164.006  1.00 11.28        H
ATOM  15819  N   LYS A1283     144.650 182.023 160.468  1.00 13.19        N
ATOM  15820  CA  LYS A1283     145.006 181.467 159.166  1.00 13.19        C
ATOM  15821  C   LYS A1283     146.316 180.686 159.221  1.00 13.19        C
ATOM  15822  O   LYS A1283     146.365 179.522 158.814  1.00 13.19        O
ATOM  15823  CB  LYS A1283     145.093 182.587 158.127  1.00 13.19        C
ATOM  15824  CG  LYS A1283     143.812 183.403 157.973  1.00 13.19        C
ATOM  15825  CD  LYS A1283     142.621 182.550 157.549  1.00 13.19        C
ATOM  15826  CE  LYS A1283     142.772 182.032 156.128  1.00 13.19        C
ATOM  15827  NZ  LYS A1283     141.541 181.336 155.660  1.00 13.19        N
ATOM  15828  H   LYS A1283     144.906 182.835 160.592  1.00 13.19        H
ATOM  15829  HA  LYS A1283     144.314 180.849 158.888  1.00 13.19        H
ATOM  15830  HB2 LYS A1283     145.800 183.197 158.388  1.00 13.19        H
ATOM  15831  HB3 LYS A1283     145.301 182.196 157.264  1.00 13.19        H
ATOM  15832  HG2 LYS A1283     143.596 183.818 158.823  1.00 13.19        H
ATOM  15833  HG3 LYS A1283     143.950 184.084 157.296  1.00 13.19        H
ATOM  15834  HD2 LYS A1283     142.530 181.790 158.143  1.00 13.19        H
ATOM  15835  HD3 LYS A1283     141.818 183.092 157.584  1.00 13.19        H
ATOM  15836  HE2 LYS A1283     142.943 182.778 155.532  1.00 13.19        H
ATOM  15837  HE3 LYS A1283     143.508 181.400 156.094  1.00 13.19        H
ATOM  15838  HZ1 LYS A1283     141.654 181.045 154.826  1.00 13.19        H
ATOM  15839  HZ2 LYS A1283     141.367 180.640 156.187  1.00 13.19        H
ATOM  15840  HZ3 LYS A1283     140.849 181.895 155.681  1.00 13.19        H
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ATOM  15843  C   GLY A1284     148.614 179.472 160.817  1.00  8.89        C
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ATOM  15849  CA  ILE A1285     147.792 178.650 162.944  1.00  7.17        C
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ATOM  15851  O   ILE A1285     147.287 176.332 162.563  1.00  7.17        O
ATOM  15852  CB  ILE A1285     147.130 179.209 164.218  1.00  7.17        C
ATOM  15853  CG1 ILE A1285     148.074 180.218 164.889  1.00  7.17        C
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ATOM  15858  HB  ILE A1285     146.323 179.676 163.957  1.00  7.17           H
ATOM  15859 HG12 ILE A1285     148.988 179.930 164.741  1.00  7.17           H
ATOM  15860 HG13 ILE A1285     147.937 181.086 164.479  1.00  7.17           H
ATOM  15861 HG21 ILE A1285     146.320 178.429 165.961  1.00  7.17           H
ATOM  15862 HG22 ILE A1285     146.105 177.480 164.722  1.00  7.17           H
ATOM  15863 HG23 ILE A1285     147.534 177.569 165.403  1.00  7.17           H
ATOM  15864 HD11 ILE A1285     148.395 181.152 166.684  1.00  7.17           H
ATOM  15865 HD12 ILE A1285     146.942 180.523 166.572  1.00  7.17           H
ATOM  15866 HD13 ILE A1285     148.197 179.584 166.838  1.00  7.17           H
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ATOM  15872  CG  ARG A1286     143.231 176.470 159.242  1.00  9.89           C
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ATOM  15874  NE  ARG A1286     140.903 176.411 158.421  1.00  9.89           N
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ATOM  15877  NH2 ARG A1286     141.495 175.183 156.558  1.00  9.89           N
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ATOM  15880  HB2 ARG A1286     143.335 177.726 160.847  1.00  9.89           H
ATOM  15881  HB3 ARG A1286     144.275 178.178 159.651  1.00  9.89           H
ATOM  15882  HG2 ARG A1286     143.849 176.092 158.598  1.00  9.89           H
ATOM  15883  HG3 ARG A1286     142.818 175.765 159.764  1.00  9.89           H
ATOM  15884  HD2 ARG A1286     141.952 178.032 158.888  1.00  9.89           H
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ATOM  15897  CD1 LEU A1287     147.851 176.712 155.156  1.00  7.01           C
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ATOM  15899  H   LEU A1287     147.029 177.576 159.238  1.00  7.01           H
ATOM  15900  HA  LEU A1287     147.273 175.572 157.596  1.00  7.01           H
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ATOM  15902  HB3 LEU A1287     149.469 177.227 158.017  1.00  7.01           H
ATOM  15903  HG  LEU A1287     149.507 175.930 156.057  1.00  7.01           H
ATOM  15904 HD11 LEU A1287     148.155 176.660 154.237  1.00  7.01           H
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ATOM  15919  HA  LEU A1288     150.860 174.195 160.193  1.00  4.51           H
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ATOM  15921  HB3 LEU A1288     151.420 174.702 162.453  1.00  4.51           H
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ATOM  15923 HD11 LEU A1288     152.952 178.016 162.044  1.00  4.51           H
ATOM  15924 HD12 LEU A1288     151.509 177.833 162.682  1.00  4.51           H
ATOM  15925 HD13 LEU A1288     152.719 176.935 163.185  1.00  4.51           H
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ATOM  15930  CA  LEU A1289     147.391 172.624 162.488  1.00  3.68           C
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ATOM  15936  CD2 LEU A1289     147.436 173.518 165.348  1.00  3.68           C
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ATOM  15939  N   LEU A1290     146.649 172.099 160.217  1.00  5.20           N
ATOM  15940  CA  LEU A1290     146.327 171.194 159.119  1.00  5.20           C
ATOM  15941  C   LEU A1290     147.524 170.322 158.765  1.00  5.20           C
ATOM  15942  O   LEU A1290     147.381 169.112 158.541  1.00  5.20           O
ATOM  15943  CB  LEU A1290     145.869 172.001 157.903  1.00  5.20           C
ATOM  15944  CG  LEU A1290     145.769 171.264 156.565  1.00  5.20           C
ATOM  15945  CD1 LEU A1290     144.792 170.105 156.660  1.00  5.20           C
ATOM  15946  CD2 LEU A1290     145.362 172.224 155.458  1.00  5.20           C
ATOM  15947  H   LEU A1290     146.616 172.934 160.012  1.00  5.20           H
ATOM  15948  HA  LEU A1290     145.598 170.613 159.388  1.00  5.20           H
ATOM  15949  HB2 LEU A1290     144.989 172.361 158.095  1.00  5.20           H
ATOM  15950  HB3 LEU A1290     146.492 172.734 157.777  1.00  5.20           H
ATOM  15951  HG  LEU A1290     146.639 170.902 156.334  1.00  5.20           H
ATOM  15952 HD11 LEU A1290     144.698 169.700 155.784  1.00  5.20           H
ATOM  15953 HD12 LEU A1290     145.135 169.453 157.292  1.00  5.20           H
ATOM  15954 HD13 LEU A1290     143.934 170.441 156.963  1.00  5.20           H
ATOM  15955 HD21 LEU A1290     145.249 171.725 154.634  1.00  5.20           H
ATOM  15956 HD22 LEU A1290     144.528 172.653 155.704  1.00  5.20           H
ATOM  15957 HD23 LEU A1290     146.058 172.891 155.349  1.00  5.20           H
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ATOM  15959  CA  ALA A1291     149.915 170.133 158.449  1.00  4.03           C
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ATOM  15962  CB  ALA A1291     151.141 171.043 158.384  1.00  4.03           C
ATOM  15963  H   ALA A1291     148.854 171.763 158.826  1.00  4.03           H
ATOM  15964  HA  ALA A1291     149.821 169.693 157.589  1.00  4.03           H
ATOM  15965  HB1 ALA A1291     151.926 170.501 158.209  1.00  4.03           H
ATOM  15966  HB2 ALA A1291     151.018 171.688 157.671  1.00  4.03           H
ATOM  15967  HB3 ALA A1291     151.238 171.502 159.233  1.00  4.03           H
ATOM  15968  N   LEU A1292     149.900 169.412 160.781  1.00  2.64           N
ATOM  15969  CA  LEU A1292     150.006 168.422 161.851  1.00  2.64           C
ATOM  15970  C   LEU A1292     148.950 167.332 161.701  1.00  2.64           C
ATOM  15971  O   LEU A1292     149.233 166.147 161.910  1.00  2.64           O
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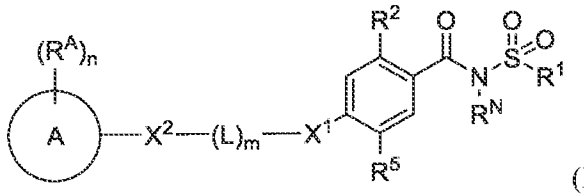
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ATOM  15983 HD13 LEU A1292     152.153 168.480 164.426  1.00  2.64           H
ATOM  15984 HD21 LEU A1292     149.923 168.414 166.478  1.00  2.64           H
ATOM  15985 HD22 LEU A1292     150.359 169.771 165.776  1.00  2.64           H
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ATOM  15987  N   ARG A1293     147.724 167.716 161.339  1.00  4.79           N
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ATOM  15989  C   ARG A1293     146.949 165.735 160.105  1.00  4.79           C
ATOM  15990  O   ARG A1293     146.681 164.538 160.261  1.00  4.79           O
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ATOM  15993  CD  ARG A1293     142.915 167.213 160.176  1.00  4.79           C
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ATOM  15996  NH1 ARG A1293     141.462 168.863 158.401  1.00  4.79           N
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ATOM  16001  HB3 ARG A1293     145.404 167.893 160.040  1.00  4.79           H
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ATOM  16003  HG3 ARG A1293     143.835 166.366 161.796  1.00  4.79           H
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ATOM  16006  HE  ARG A1293     143.422 169.073 160.724  1.00  4.79           H
ATOM  16007 HH11 ARG A1293     141.335 168.013 158.409  1.00  4.79           H
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ATOM  16011  N   LYS A1294     147.501 166.198 158.981  1.00  4.64           N
ATOM  16012  CA  LYS A1294     147.821 165.277 157.895  1.00  4.64           C
ATOM  16013  C   LYS A1294     148.866 164.252 158.324  1.00  4.64           C
ATOM  16014  O   LYS A1294     148.860 163.112 157.846  1.00  4.64           O
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ATOM  16016  CG  LYS A1294     147.204 166.400 155.686  1.00  4.64           C
ATOM  16017  CD  LYS A1294     147.503 167.692 154.946  1.00  4.64           C
ATOM  16018  CE  LYS A1294     146.398 168.037 153.962  1.00  4.64           C
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ATOM  16020  H   LYS A1294     147.695 167.021 158.828  1.00  4.64           H
ATOM  16021  HA  LYS A1294     147.017 164.795 157.644  1.00  4.64           H
ATOM  16022  HB2 LYS A1294     148.712 166.884 156.968  1.00  4.64           H
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HETATM19178  C02 DRG A   7     131.050 176.792 195.152  1.00  7.50           C
HETATM19179  C03 DRG A   7     130.616 175.808 192.865  1.00  7.50           C
HETATM19180  C04 DRG A   7     129.142 176.240 192.831  1.00  7.50           C
HETATM19181  C05 DRG A   7     128.477 175.993 191.476  1.00  7.50           C
HETATM19182  C06 DRG A   7     128.918 174.675 190.854  1.00  7.50           C
HETATM19183  C07 DRG A   7     130.430 174.570 190.657  1.00  7.50           C
HETATM19184  C08 DRG A   7     131.232 175.614 191.448  1.00  7.50           C
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HETATM19186  C10 DRG A   7     133.547 176.289 189.533  1.00  7.50           C
HETATM19187  C11 DRG A   7     134.545 176.378 188.553  1.00  7.50           C
HETATM19188  C12 DRG A   7     135.619 175.486 188.570  1.00  7.50           C
HETATM19189  C13 DRG A   7     135.688 174.521 189.557  1.00  7.50           C
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HETATM19193  C17 DRG A   7     135.360 171.460 185.297  1.00  7.50           C
HETATM19194  C18 DRG A   7     135.187 170.072 185.268  1.00  7.50           C
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HETATM19196  C20 DRG A   7     133.788 167.444 183.193  1.00  7.50           C
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HETATM19198  C22 DRG A   7     133.537 165.405 184.726  1.00  7.50           C
HETATM19199  C23 DRG A   7     133.493 163.898 184.504  1.00  7.50           C
HETATM19200  C24 DRG A   7     133.407 163.689 182.991  1.00  7.50           C
HETATM19201  C25 DRG A   7     133.319 165.080 182.381  1.00  7.50           C
HETATM19202  C26 DRG A   7     134.165 170.292 183.086  1.00  7.50           C
HETATM19203  C27 DRG A   7     134.343 171.682 183.125  1.00  7.50           C
HETATM19204  F01 DRG A   7     136.699 173.644 189.613  1.00  7.50           F
HETATM19205  N01 DRG A   7     131.467 176.755 193.714  1.00  7.50           N
HETATM19206  N02 DRG A   7     132.645 175.185 191.535  1.00  7.50           N
HETATM19207  N03 DRG A   7     136.090 175.178 185.927  1.00  7.50           N
HETATM19208  N04 DRG A   7     135.191 173.632 184.427  1.00  7.50           N
HETATM19209  O01 DRG A   7     137.932 174.656 187.582  1.00  7.50           O
HETATM19210  O02 DRG A   7     137.201 177.017 187.210  1.00  7.50           O
HETATM19211  O03 DRG A   7     134.471 168.141 184.237  1.00  7.50           O
HETATM19212  S01 DRG A   7     136.862 175.608 187.332  1.00  7.50           S
HETATM19213  S02 DRG A   7     136.059 172.430 186.521  1.00  7.50           S
HETATM19214  H01 DRG A   7     132.140 178.068 192.308  1.00  7.50           H
HETATM19215  H02 DRG A   7     132.258 178.612 193.781  1.00  7.50           H
HETATM19216  H03 DRG A   7     130.833 178.586 193.076  1.00  7.50           H
HETATM19217  H04 DRG A   7     130.205 177.263 195.226  1.00  7.50           H
HETATM19218  H05 DRG A   7     130.968 175.879 195.470  1.00  7.50           H
HETATM19219  H06 DRG A   7     131.741 177.250 195.655  1.00  7.50           H
HETATM19220  H07 DRG A   7     130.674 174.955 193.323  1.00  7.50           H
HETATM19221  H08 DRG A   7     128.663 175.742 193.512  1.00  7.50           H
HETATM19222  H09 DRG A   7     129.020 177.176 193.055  1.00  7.50           H
HETATM19223  H10 DRG A   7     127.513 176.002 191.584  1.00  7.50           H
HETATM19224  H11 DRG A   7     128.694 176.719 190.871  1.00  7.50           H
HETATM19225  H12 DRG A   7     128.469 174.540 190.004  1.00  7.50           H
HETATM19226  H13 DRG A   7     128.628 173.952 191.430  1.00  7.50           H
HETATM19227  H14 DRG A   7     130.710 173.671 190.891  1.00  7.50           H
HETATM19228  H15 DRG A   7     130.636 174.666 189.714  1.00  7.50           H
HETATM19229  H16 DRG A   7     131.166 176.464 190.985  1.00  7.50           H
HETATM19230  H17 DRG A   7     132.895 174.807 192.301  1.00  7.50           H
HETATM19231  H18 DRG A   7     132.849 176.901 189.489  1.00  7.50           H
HETATM19232  H19 DRG A   7     134.483 177.033 187.895  1.00  7.50           H
HETATM19233  H20 DRG A   7     134.769 173.777 191.182  1.00  7.50           H
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HETATM19234  H21 DRG A   7      135.861 175.820 185.356  1.00  7.50           H
HETATM19235  H22 DRG A   7      135.468 169.542 185.979  1.00  7.50           H
HETATM19236  H23 DRG A   7      134.133 167.697 182.322  1.00  7.50           H
HETATM19237  H24 DRG A   7      132.839 167.640 183.238  1.00  7.50           H
HETATM19238  H25 DRG A   7      134.998 165.788 183.346  1.00  7.50           H
HETATM19239  H26 DRG A   7      132.645 165.735 184.918  1.00  7.50           H
HETATM19240  H27 DRG A   7      134.109 165.644 185.471  1.00  7.50           H
HETATM19241  H28 DRG A   7      134.295 163.478 184.850  1.00  7.50           H
HETATM19242  H29 DRG A   7      132.737 163.498 184.959  1.00  7.50           H
HETATM19243  H30 DRG A   7      132.645 163.141 182.744  1.00  7.50           H
HETATM19244  H31 DRG A   7      134.204 163.234 182.679  1.00  7.50           H
HETATM19245  H32 DRG A   7      132.390 165.343 182.297  1.00  7.50           H
HETATM19246  H33 DRG A   7      133.722 165.117 181.499  1.00  7.50           H
HETATM19247  H34 DRG A   7      133.761 169.928 182.332  1.00  7.50           H
HETATM19248  H35 DRG A   7      134.062 172.211 182.414  1.00  7.50           H
HETATM19249  H36 DRG A   7      132.274 176.379 193.694  1.00  7.50           H
TER
END
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WE CLAIM:

1. A compound of Formula I:



(I)

and pharmaceutically acceptable salts thereof, wherein:

R^1 is selected from a first set of moieties consisting of C_{1-8}alkyl, C_{3-12}cycloalkyl, C-linked C_{2-11}heterocycloalkyl, C_{3-12}carbocycle, aryl, heteroaryl, and $-NR^{1A}R^{1B}$, wherein:

R^{1A} and R^{1B} are selected from H, C_{1-8}alkyl, C_{3-8}cycloalkyl, C_{1-8}haloalkyl, or R^{1A} and R^{1B} together with the nitrogen atom to which they are both bonded form a 3 to 10 membered heterocyclic group;

any of the first set of moieties, R^{1A}, or R^{1B}, is optionally substituted with one or more substituents selected from a second set of moieties consisting of:

C_{1-8}alkyl, C_{2-8}alkenyl, C_{3-8}cycloalkyl, C_{1-8}haloalkyl, aryl, (aryl)C_{1-8}alkyl, heteroaryl, (heteroaryl)C_{1-8}alkyl, C_{2-11}heterocycloalkyl, (C_{2-11}heterocycloalkyl)C_{1-8}alkyl, F, Cl, Br, I, –OH, –CN, $–NO_2$, =O, aminocarbonyl, $–X^{R1}NR^{R1a}R^{R1b}$, $–X^{R1}OR^{R1a}$, and $–X^{R1}SR^{R1a}$, wherein:

X^{R1} is selected from the group consisting of C(=O), C_{1-4} alkylene, C_{1-4}heteroalkylene, C_{2-4}alkenylene and C_{2-4} alkynylene, or is absent; and

R^{R1a} and R^{R1b} are independently selected from a third set of moieties consisting of: H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{1-8}haloalkyl, C_{3-8}cycloalkyl, C_{3-12}carbocycle, (C_{3-8} cycloalkyl)C_{1-8} alkyl, aryl, (aryl)C_{1-8}alkyl, heteroaryl, (heteroaryl)C_{1-8}alkyl, C_{2-11}heterocycloalkyl, and (C_{2-11}heterocycloalkyl)C_{1-8}alkyl,

or R^{R1a} and R^{R1b} together with the nitrogen atom to which they are both bonded form a 3 to 10 membered heterocyclic group;

and

wherein any of the second set of moieties, R^{R1a}, or R^{R1b}, where present, are each optionally substituted by one or more groups independently selected from: C_{1-8} alkyl, C_{1-8}haloalkyl, F, Cl, Br, I, -OH, -CN, aryl, C_{1-8}haloalkyl-substituted aryl, C_{1-8}alkoxy, C_{1-8}alkanoyl, C_{1-8}alkoxycarbonyl, C_{3-8}cycloalkyl, C_{2-11}heterocycloalkyl, amino, (C_{1-3}alkyl)amino, di(C_{1-3}alkyl)-amino, C_{1-3}alkylamido, C_{1-3}alkylcarboxy, and $-NO_2$;

R^N is hydrogen, C_{1-4} alkyl, or C_{1-4}haloalkyl;

R^2 is selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl and C_{1-8} alkoxy;

R^5 is selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} haloalkyl, C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{2-11} heterocycloalkyl, phenyl and 5-6 membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O and S, wherein said 5-6 membered heteroaryl, C_{1-8} alkyl, C_{3-8} cycloalkyl or C_{2-11} heterocycloalkyl is further optionally substituted with from 1 to 3 substituents selected from F, Cl, Br, I, -OH , =O, C_{3-6} cycloalkyl, -CN, C_{1-4} alkyl, -C_{1-4} alkyl-O-C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} alkoxy;

L is a linker selected from the group consisting of C_{1-4} alkylene, C_{2-4} alkenylene, C_{2-4} alkynylene, and C_{1-4} heteroalkylene, wherein L is optionally substituted with from 1 to 3 substituents selected from the group consisting of =O, -OH, -OCH_2-phenyl, C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} acyl;

m is 0 or 1;

X^1 and X^2 are each independently selected from the group consisting of, –O–, –S(O) –, –$S(O)_2$– and –$N(R^X)$–, wherein R^x is H, C_{1-8} alkyl, C_{1-8} acyl and –$S(O)_2$(C_{1-8} alkyl), or is absent;

and wherein if m is 0 then at least one of X^1 or X^2 is absent;

n is an integer from 0 to 5;

A is selected from the group consisting of: hydrogen, C_{1-8}alkyl, C_{1-8}haloalkyl, C_{3-12} cycloalkyl, and aryl, and wherein if A is hydrogen then n is 0; and

each R^A is independently selected from the group consisting of C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, -NO_2, and =O.

2. The compound or pharmaceutically acceptable salt of claim 1, wherein R^N is hydrogen.

3. The compound or pharmaceutically acceptable salt of claim 1, wherein n is 0.

4. The compound or pharmaceutically acceptable salt of any one of claims 1 – 3, wherein A is C_{5-6} cycloalkyl.

5. The compound or pharmaceutically acceptable salt of any one of claims 1 – 3, wherein A is cyclopentyl.

6. The compound or pharmaceutically acceptable salt of any one of claims 1 – 5, wherein $\mathbf{X^1}$ is -O-.

7. The compound or pharmaceutically acceptable salt of any one of claims 1 – 6, wherein $\mathbf{X^2}$ is absent.

8. The compound or pharmaceutically acceptable salt of any one of claims 1 – 7, wherein **L** is $C_{1\text{-}4}$ alkylene.

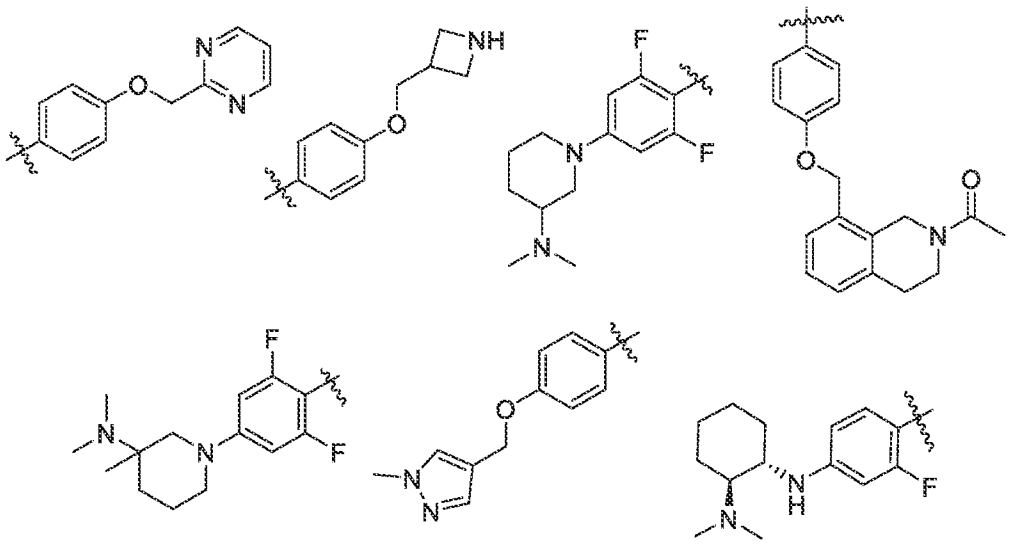
9. The compound or pharmaceutically acceptable salt of any one of claims 1 – 8, wherein **L** is methylene.

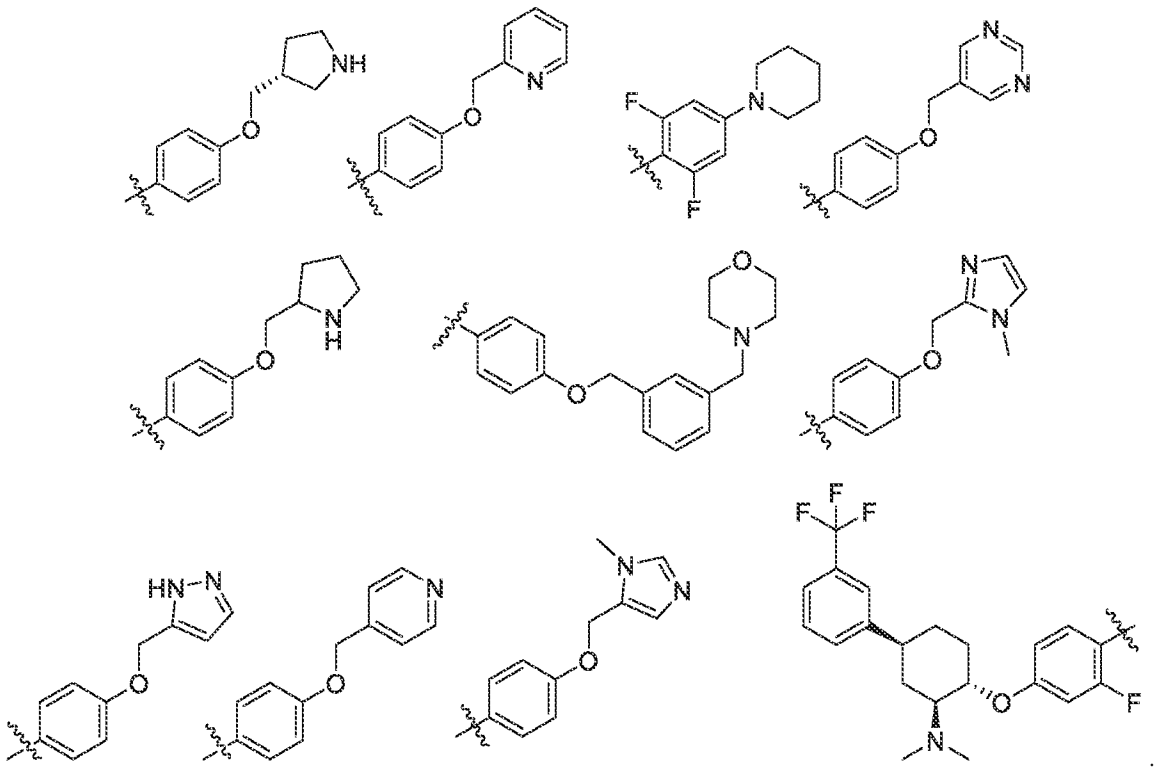
10. The compound or pharmaceutically acceptable salt of any one of claims 1 – 9, wherein $\mathbf{R^2}$ is H or F.

11. The compound or pharmaceutically acceptable salt of any one of claims 1 – 10, wherein $\mathbf{R^5}$ is selected from the group consisting of H, F, Cl, ethyl, isopropyl, methoxy, and cyclopropyl.

12. The compound or pharmaceutically acceptable salt of any one of claims 1 – 10, wherein $\mathbf{R^5}$ is methyl, Cl, or cyclopropyl.

13. The compound or pharmaceutically acceptable salt of any one of claims 1 – 12, wherein $\mathbf{R^1}$ is selected from the group consisting of:





and

14. The compound or pharmaceutically acceptable salt of claim 1, which is selected from the group consisting of:

Ex. 1: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide;

Ex. 2: 4-(cyclopentylmethoxy)-2-fluoro-5-methyl-N-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide;

Ex. 3: 4-(cyclopentylmethoxy)-5-ethyl-2-fluoro-N-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl) sulfonyl) benzamide;

Ex. 4: 4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluoro-N-((4-((1-methylazetidin-3-yl)oxy) piperidin-1-yl) sulfonyl) benzamide;

Ex. 5: 4-(cyclopentylmethoxy)-2-fluoro-5-isopropyl-N-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide;

Ex. 6: 4-(cyclopentylmethoxy)-2-fluoro-5-methoxy-N-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl) sulfonyl) benzamide;

Ex. 7: 5-cyclobutyl-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide;

Ex. 9: 5-cyclopropyl-4-(cyclopropylmethoxy)-2-fluoro-N-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide;

Ex. 10: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((1-isopropylazetidin-3-yl)oxy)piperid;in-1-yl)sulfonyl)benzamide;

Ex. 11: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((1-(oxetan-3-yl)azetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide;

Ex. 12: 5-chloro-4-(cyclopentylmethoxy)-N-((4-((1-cyclopropylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)-2-fluorobenzamide;

Ex. 13: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((1-(2,2,2-trifluoroethyl)azetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide;

Ex. 14: 5-chloro-4-(cyclopentylmethoxy)-N-((3,4-dihydroquinolin-1(2H)-yl)sulfonyl)-2-fluorobenzamide;

Ex. 15: 5-chloro-4-(cyclopentylmethoxy)-N-((3, 4-dihydro-1, 8-naphthyridin-1(2H)-yl)sulfonyl)-2-fluorobenzamide;

Ex. 16: (S)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((3-methyl-3,4-dihydroquinolin-1(2H)-yl)sulfonyl)benzamide;

Ex. 17: (R)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((3-methyl-3,4-dihydroquinolin-1(2H)-yl)sulfonyl)benzamide;

Ex. 18: (R)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((2-methyl-3,4-dihydro-quinolin-1(2H)-yl)sulfonyl)benzamide;

Ex. 19: 5-chloro-4-(cyclopentylmethoxy)-N-((3,4-dihydroisoquinolin-2(1H)-yl)sulfonyl)-2-fluorobenzamide;

Ex. 20: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-methoxypiperidin-1-yl)sulfonyl)benzamide;

Ex. 21: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(piperidin-1-ylsulfonyl)benzamide;

Ex. 22: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(pyrrolidin-1-ylsulfonyl)-benzamide;

Ex. 23: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((hexahydro-1H-pyrazino[1,2-a]pyrazin-2(6H)-yl)sulfonyl)benzamide *(CHECK NAME)*;

Ex. 24: (R)-N-((2-(aminomethyl)morpholino)sulfonyl)-5-chloro-4-(cyclopentyl-methoxy)-2-fluorobenzamide;

Ex. 25: (R)-N-((2-(aminomethyl)morpholino)sulfonyl)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzamide;

Ex. 26: (R)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((2-((methylamino) methyl)morpholino)sulfonyl) benzamide;

Ex. 27: (R)-N-((3-(aminomethyl)piperidin-1-yl)sulfonyl)-5-chloro-4-(cyclopentyl-methoxy)-2-fluorobenzamide;

Ex. 28: (R)-5-chloro-4-(cyclopentylmethoxy)-N-((2-((dimethylamino)¬methyl)-morpholino)sulfonyl)-2-fluorobenzamide;

Ex. 29: (R)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluoro-N-((4-(pyrrolidin-3-yloxy)piperidin-1-yl)sulfonyl)benzamide;

Ex. 30: (S)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluoro-N-((4-(pyrrolidin-3-yloxy)piperidin-1-yl)sulfonyl)benzamide;

Ex. 31: (R)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((3-(pyrrolidin-3-yloxy)azetidin-1-yl)sulfonyl)benzamide;

Ex. 36: (R)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-(pyrrolidin-3-yloxy)piperidin-1-yl)sulfonyl)benzamide;

Ex. 37: (S)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-(pyrrolidin-3-yloxy)piperidin-1-yl)sulfonyl)benzamide;

Ex. 38: (R)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((1-methylpyrrolidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide;

Ex. 40: N-((4-(azetidin-3-ylmethyl)piperidin-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 41: N-((4-(benzyloxy)piperidin-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 44: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(((4aR,8aR)-2-oxo-1-phenylhexahydro-1H-pyrido[3,4-b][1,4]oxazin-6(7H)-yl)sulfonyl)benzamide;

Ex. 45: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(((4aS,8aS)-2-oxo-1-phenylhexahydro-1H-pyrido[3,4-b][1,4]oxazin-6(7H)-yl)sulfonyl)benzamide;

Ex. 46: N-((4-(azetidin-3-yloxy)piperidin-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 47: N-((4-(azetidin-3-yloxy)piperidin-1-yl)sulfonyl)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzamide;

Ex. 48: (S)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((3-(piperidin-3-yloxy) azetidin-1-yl) sulfonyl)benzamide;

Ex. 49: (R)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((3-(piperidin-3-yloxy)-azetidin-1-yl)sulfonyl)benzamide;

Ex. 50: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((3-(piperidin-4-yloxy) azetidin-1-yl)sulfonyl)benzamide;

Ex. 51: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-(piperidin-3-yloxy)piperidin-1-yl)sulfonyl)benzamide 2,2,2-trifluoroacetate;

Ex. 52: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((1-methylpiperidin-3-yl)oxy)piperidin-1-yl)sulfonyl) benzamide;

Ex. 53: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-(piperidin-4-yloxy) piperidin-1-yl)sulfonyl) benzamide;

Ex. 57: 3-chloro-4-(cyclopentylmethoxy)-N-((4-(((1S,2S)-2-(dimethylamino)-cyclohexyl)amino)-2-fluorophenyl)sulfonyl)benzamide;

Ex. 58: 5-chloro-4-(cyclopentylmethoxy)-N-((2,6-difluoro-4-(piperidin-1-yl)phenyl)-sulfonyl)-2-fluorobenzamide;

Ex. 59: 5-chloro-4-(cyclopentylmethoxy)-N-((4-(((1S,2S)-2-(dimethylamino)-cyclohexyl)amino)-2-fluorophenyl)sulfonyl)-2-fluorobenzamide;

Ex. 62: 5-chloro-4-(cyclopentylmethoxy)-N-((4-(3-(dimethylamino)piperidin-1-yl)-2,6-difluorophenyl)sulfonyl)-2-fluorobenzamide;

Ex. 63: 4-(cyclopentylmethoxy)-5-cyclopropyl-N-((4-(((1S,2S)-2-(dimethylamino)-cyclohexyl)amino)-2-fluorophenyl)sulfonyl)-2-fluorobenzamide;

Ex. 64: 5-chloro-4-(cyclopentylmethoxy)-N-((4-(((1S,2S)-2-(dimethylamino)-cyclohexyl)amino)phenyl)sulfonyl)-2-fluorobenzamide;

Ex. 65: 4-(cyclopentylmethoxy)-5-cyclopropyl-N-((4-(((1S,2S)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorophenyl)sulfonyl)-2-fluorobenzamide;

Ex. 66: 5-chloro-4-(cyclopentylmethoxy)-N-((4-(((1S,2S)-2-(dimethylamino)-cyclohexyl)oxy)-2-fluorophenyl)sulfonyl)-2-fluorobenzamide;

Ex. 69: (R)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-(pyrrolidin-3-yloxy)-phenyl)sulfonyl)benzamide;

Ex. 70: N-((4-(benzyloxy)-2-fluorophenyl)sulfonyl)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzamide;

Ex. 72: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((1-(5-fluoro-2-methoxy-phenyl)isoquinolin-6-yl)sulfonyl)benzamide;

Ex. 74: 5-cyclopropyl-N-((4-(((1S,2S,4S)-2-(dimethylamino)-4-(3-(trifluoro-methyl)-phenyl)cyclohexyl)oxy)-2-fluorophenyl)sulfonyl)-2-fluoro-4-methoxybenzamide;

Ex. 75: 5-cyclopropyl-N-((4-(((1S,2S,4S)-2-(dimethylamino)-4-(3-(trifluoromethyl)-phenyl)cyclohexyl)oxy)-2-fluorophenyl)sulfonyl)-2-fluorobenzamide;

Ex. 76: 5-chloro-4-(cyclopentylmethoxy)-N-((4-(3-(dimethylamino)-3-methylpiperidin-1-yl)-2,6-difluorophenyl)sulfonyl)-2-fluorobenzamide;

Ex. 78: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(phenylsulfonyl)benzamide;

Ex. 79: 5-chloro-4-(cyclopentylmethoxy)-N-((2,6-difluorophenyl)sulfonyl)-2-fluorobenzamide;

Ex. 80: 5-chloro-N-((5-chloro-2-fluorophenyl)sulfonyl)-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 81: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-methoxyphenyl)¬sulfonyl)-benzamide;

Ex. 82: 5-chloro-N-(cyclohexylsulfonyl)-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 83: N-((4-(benzyloxy)phenyl)sulfonyl)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzamide;

Ex. 84: N-((4-(benzylamino)phenyl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 85: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-(pyridin-4-ylmethoxy)-phenyl)sulfonyl)benzamide;

Ex. 86: trans-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-methoxy-cyclohexyl)¬sulfonyl)¬benz-amide;

Ex. 87: cis-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-methoxy-cyclohexyl)sulfonyl)benzamide;

Ex. 204: 4-(cyclopentylmethoxy)-5-cyclopropyl-N-((4-(((1S,2S)-2-(dimethylamino)cyclohexyl)amino)-2,6-difluorophenyl)sulfonyl)-2-fluorobenzamide

Ex. 205: 5-chloro-4-(cyclopentylmethoxy)-N-((4-(3-(dimethylamino)piperidin-1-yl)-2-fluorophenyl)sulfonyl)-2-fluorobenzamide

Ex. 207: 4-(cyclopentylmethoxy)-5-cyclopropyl-N-((4-(3-(dimethylamino)piperidin-1-yl)-2,6-difluorophenyl)sulfonyl)-2-fluorobenzamide

Ex. 208: 5-chloro-N-((4-(cyclohexylamino)-2-fluorophenyl)sulfonyl)-4-(cyclopentylmethoxy)-2-fluorobenzamide

Ex. 212: (S)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((3-(piperidin-4-yloxy)pyrrolidin-1-yl)sulfonyl)benzamide;

Ex. 213: (R)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((3-(piperidin-4-yloxy)pyrrolidin-1-yl)sulfonyl)benzamide;

Ex. 217: N-(((1R,5S)-1-amino-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide 2,2,2-trifluoroacetate;

Ex. 218: N-(((1S,5R)-1-amino-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide 2,2,2-trifluoroacetate;

Ex. 219: (S)-N-((3-aminoazepan-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 220: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(((3aS,6aR)-hexahydro-cyclopenta[b]pyrrol-1(2H)-yl)sulfonyl)benzamide;

Ex. 221: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(((3aR,6aS)-hexahydro-cyclopenta[b]pyrrol-1(2H)-yl)sulfonyl)benzamide;

Ex. 222: (R)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((2-methylpyrrolidin-1-yl)sulfonyl)benzamide;

Ex. 223: (S)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((2-methylpyrrolidin-1-yl)sulfonyl)-benzamide;

Ex. 224: (S)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((2-methylpiperidin-1-yl)sulfonyl)benzamide;

Ex. 225: (R)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((2-methylpiperidin-1-yl)sulfonyl)benzamide;

Ex. 226: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((3-(methylamino)-azetidin-1-yl)sulfonyl)benzamide;

Ex. 227: N-(azepan-1-ylsulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 228: N-((1-oxa-6-azaspiro[3.3]heptan-6-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 229: N-((4-azaspiro[2.4]heptan-4-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 230: *N*-(((1*R*,5*S*)-3-azabicyclo[3.2.1]octan-3-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 231: N-((1S,6R)-3,8-diazabicyclo[4.2.0]octan-3-ylsulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 232: (S)-N-((3-(aminomethyl)pyrrolidin-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 233: N-((3-aminoazetidin-1-yl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 234: 5-chloro-4-(cyclopentylmethoxy)-N-((3-(dimethylamino)-azetidin-1-yl)sulfonyl)-2-fluorobenzamide;

Ex. 236: 4-(benzyloxy)-5-cyclopropyl-2-fluoro-N-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide;

Ex. 237: 5-cyclopropyl-2-fluoro-4-isobutoxy-*N*-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide;

Ex. 238: 5-cyclopropyl-2-fluoro-N-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)-4-(2,2,2-trifluoroethoxy)benzamide;

Ex. 239: 5-chloro-4-(4-chloro-3-(trifluoromethyl)phenoxy)-2-fluoro-N-((4-((1-methylazetidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide;

Ex. 241: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((2-fluorophenyl)sulfonyl)benzamide;

Ex. 242: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(o-tolylsulfonyl)benzamide;

Ex. 243: 5-chloro-4-(cyclopentylmethoxy)-*N*-((4-ethylphenyl)sulfonyl)-2-fluorobenzamide;

Ex. 244: 5-chloro-4-(cyclopentylmethoxy)-N-((3-ethylphenyl)sulfonyl)-2-fluorobenzamide;

Ex. 245: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((3-methoxy-phenyl)sulfonyl)benzamide;

Ex. 246: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((2-methoxy-phenyl)sulfonyl)benzamide;

Ex. 247: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(isopropylsulfonyl)benzamide;

Ex. 248: (S)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((1-methoxypropan-2-yl)sulfonyl)-benzamide;

Ex. 249: (R)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((1-methoxypropan-2-yl)sulfonyl)-benzamide;

Ex. 250: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(((1S,2S)-2-methylcyclo-propyl)sulfonyl)benzamide;

Ex. 251: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(((1R,2R)-2-methylcyclopropyl)¬sulfonyl)-benzamide;

Ex. 252: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-methylthiophen-2-yl)sulfonyl)benzamide;

Ex. 253: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((3-(3-(trifluoromethyl)phenoxy)propyl)sulfonyl)benzamide;

Ex. 254: (S)-N-(sec-butylsulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 255: (R)-N-(sec-butylsulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 256: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(spiro[2.3]hexan-1-ylsulfonyl)benzamide;

Ex. 259: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-4-yl)sulfonyl)benzamide;

Ex. 260: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((3-methylbenzyl)oxy)phenyl)sulfonyl)benzamide;

Ex. 261: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((5,6,7,8-tetrahydronaphthalen-2-yl)sulfonyl)benzamide;

Ex. 262: 5-chloro-4-(cyclopentylmethoxy)-N-((2,3-dihydro-1H-inden-5-yl)sulfonyl)-2-fluorobenzamide;

Ex. 263: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-phenoxyphenyl)sulfonyl)benzamide;

Ex. 264: 5-chloro-N-((4-((2-chlorobenzyl)oxy)phenyl)sulfonyl)-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 265: 5-chloro-N-(chroman-6-ylsulfonyl)-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 266: 5-chloro-4-(cyclopentylmethoxy)-N-(((2,3-dihydro-1H-inden-2-yl)methyl)sulfonyl)-2-fluorobenzamide;

Ex. 267: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((1,2,3,4-tetrahydroquinolin-7-yl)sulfonyl)benzamide;

Ex. 268: 5-chloro-4-(cyclopentylmethoxy)-N-((2,3-difluorobenzyl)-sulfonyl)-2-fluorobenzamide;

Ex. 269: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((1-(2-fluorophenyl)-1H-pyrazol-4-yl)sulfonyl)benzamide;

Ex. 270: (S)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((2-methyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)benzamide;

Ex. 271: 5-chloro-4-(cyclopentylmethoxy)-N-((2,3-dihydrobenzofuran-5-yl)sulfonyl)-2-fluorobenzamide;

Ex. 272: 5-chloro-N-((4-cyano-2-fluorophenyl)sulfonyl)-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 273: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((quinolin-6-ylmethyl)sulfonyl)benzamide;

Ex. 274: N-((2-(benzyloxy)ethyl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 275: 5-chloro-4-(cyclopentylmethoxy)-N-((3,4-dihydronaphthalen-2-yl)sulfonyl)-2-fluorobenzamide;

Ex. 276: 5-chloro-4-(cyclopentylmethoxy)-N-((4-cyclopropoxyphenyl)sulfonyl)-2-fluorobenzamide;

Ex. 277: (S)-5-(N-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)sulfamoyl)-2,3-dihydrobenzofuran-2-carboxamide;

Ex. 278: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((1-fluoronaphthalen-2-yl)sulfonyl)benzamide;

Ex. 279: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((8-fluoroquinolin-5-yl)sulfonyl)benzamide;

Ex. 280: 5-chloro-N-((4-cyano-3-(trifluoromethyl)phenyl)sulfonyl)-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 281: 5-chloro-4-(cyclopentylmethoxy)-N-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfonyl)-2-fluorobenzamide;

Ex. 282: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(indolin-6-ylsulfonyl)benzamide;

Ex. 283: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-(trifluoromethyl)phenyl)sulfonyl)benzamide;

Ex. 284: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((trans-2-phenylcyclopropyl)sulfonyl)benzamide;

Ex. 285: 5-chloro-4-(cyclopentylmethoxy)-N-((6-ethoxypyridin-3-yl)sulfonyl)-2-fluorobenzamide;

Ex. 286: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)phenyl)sulfonyl)benzamide;

Ex. 287: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-*N*-((4-(2,2,2-trifluoroethoxy)phenyl)sulfonyl)benzamide;

Ex. 288: 5-chloro-N-((4-(4-chlorophenoxy)phenyl)sulfonyl)-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 289: 5-chloro-4-(cyclopentylmethoxy)-N-((3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)sulfonyl)-2-fluorobenzamide;

Ex. 290: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(naphthalen-2-ylsulfonyl)benzamide;

Ex. 291: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((1-(2-methoxyphenyl)-1H-pyrazol-4-yl)sulfonyl)benzamide;

Ex. 292: N-((4-((1H-1,2,4-triazol-1-yl)methyl)phenyl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide

Ex. 293: 5-chloro-N-((2-chloro-4-(trifluoromethoxy)phenyl)sulfonyl)-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 294: N-((4-(benzyloxy)phenyl)sulfonyl)-5-chloro-4-(cyclopentyl-methoxy)-2-fluorobenzamide;

Ex. 295: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-(pyrimidin-2-ylmethoxy)phenyl)sulfonyl)benzamide;

Ex. 296: N-((4-(azetidin-3-ylmethoxy)phenyl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 297: N-((4-((2-acetyl-1,2,3,4-tetrahydroisoquinolin-8-yl)methoxy)phenyl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 298: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((3-fluorobenzyl)oxy)-phenyl)sulfonyl)-benzamide;

Ex. 299: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((1-methyl-1H-pyrazol-4-yl)methoxy)phenyl)sulfonyl)benzamide;

Ex. 300: N-((4-((3-(aminomethyl)benzyl)oxy)phenyl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 301: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-(pyridin-2-ylmethoxy)phenyl)sulfonyl)benzamide;

Ex. 302: (R)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-(pyrrolidin-3-ylmethoxy)phenyl)sulfonyl)benzamide;

Ex. 303: 5-chloro-4-(cyclopentylmethoxy)-N-((4-((3,5-dimethyl-benzyl)oxy)phenyl)sulfonyl)-2-fluorobenzamide;

Ex. 304: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-(pyrimidin-5-ylmethoxy)phenyl)sulfonyl)benzamide;

Ex. 305: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-(pyrrolidin-2-ylmethoxy)phenyl)sulfonyl)benzamide;

Ex. 306: 5-chloro-4-(cyclopentylmethoxy)-N-((4-((3,5-dimethoxybenzyl)oxy)phenyl)sulfonyl)-2-fluorobenzamide;

Ex. 307: 5-chloro-4-(cyclopentylmethoxy)-N-((4-((3,5-difluorobenzyl)oxy)phenyl)sulfonyl)-2-fluorobenzamide;

Ex. 308: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((3-methoxybenzyl)oxy)phenyl)sulfonyl)benzamide;

Ex. 309: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((4-methoxybenzyl)oxy)phenyl)sulfonyl)benzamide;

Ex. 310: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-(pyridin-3-ylmethoxy)phenyl)sulfonyl)benzamide;

Ex. 311: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((3-(morpholinomethyl)benzyl)oxy)phenyl)sulfonyl)benzamide;

Ex. 312: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((1-methyl-1H-imidazol-2-yl)methoxy)phenyl)sulfonyl)benzamide;

Ex. 313: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((4-methylbenzyl)oxy)phenyl)sulfonyl)benzamide;

Ex. 314: N-((4-(3-aminopropoxy)phenyl)sulfonyl)-5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamide;

Ex. 315: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((1-methyl-1H-pyrazol-5-yl)methoxy)phenyl)sulfonyl)benzamide;

Ex. 316: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((1-methyl-1H-imidazol-5-yl)methoxy)phenyl)sulfonyl)benzamide;

Ex. 317: 5-chloro-4-(cyclopentylmethoxy)-N-((4-((2,4-difluorobenzyl)oxy)phenyl)sulfonyl)-2-fluorobenzamide;

Ex. 318: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((2-methoxybenzyl)oxy)phenyl)sulfonyl)benzamide;

Ex. 319: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((4-fluorobenzyl)oxy)phenyl)sulfonyl)benzamide;

Ex. 320: 4-(cyclopentylmethoxy)-5-cyclopropyl-N-((4-(((1S,2S)-2-(dimethylamino)cyclohexyl)amino)-2-fluorophenyl)sulfonyl)-2-fluorobenzamide;

Ex. 321: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((octahydro-2,7-naphthyridin-2(1H)-yl)sulfonyl)benzamide;

Ex. 322: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(pyrrolidin-3-ylsulfonyl)-benzamide;

Ex. 323: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((1-methylpyrrolidin-3-yl)sulfonyl)benzamide;

Ex. 324: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-(piperidin-4-ylsulfonyl)-benzamide;

Ex. 325: 5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-(pyrrolidin-3-yloxy)phenyl)sulfonyl)benzamide;

Ex. 326: (S)-5-chloro-4-(cyclopentylmethoxy)-2-fluoro-N-((4-((1-methylpyrrolidin-3-yl)oxy)piperidin-1-yl)sulfonyl)benzamide;

Ex. 327: tert-butyl 6-((N-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzoyl)-sulfamoyl)amino)bicyclo[3.1.0]hexane-3-carboxylate;

Ex. 328: 5-chloro-4-(cyclopentylmethoxy)-N-(cyclopropylsulfonyl)-2-fluorobenzamide;

Ex. 329: 5-chloro-4-(cyclopentylmethoxy)-N-((4-(dimethylamino)piperidin-1-yl)sulfonyl)-2-fluorobenzamide;

Ex. 330: N-((2-(aminomethyl)morpholino)sulfonyl)-4-(cyclopentylmethoxy)-5-cyclopropyl-2-fluorobenzamide; and

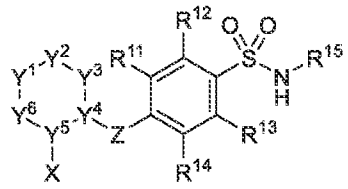
Ex. 331: 4-(cyclopentylmethoxy)-5-cyclopropyl-N-((4-(((1S,2S)-2-(dimethylamino)cyclohexyl)oxy)piperidin-1-yl)sulfonyl)-2-fluorobenzamide,

or pharmaceutically acceptable salts thereof.

15. A compound or pharmaceutically acceptable salt thereof, having the formula:

Ex. 107: (R)-2-(5-chloro-4-(cyclopentylmethoxy)-2-fluorobenzamido)-2-cyclohexylacetic acid.

16. A compound of Formula II:



II

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{R^{11}}$, $\mathbf{R^{12}}$, $\mathbf{R^{13}}$, and $\mathbf{R^{14}}$ are each independently selected from hydrogen, C_1-C_6 alkyl, cyano, C_3-C_6 cycloalkyl, hydroxy, C_1-C_6 alkoxy, $-NH_2$, $-NHR$, $-NR_2$, $-SR$, $-S(O)R$, $-SO_2R$, SO_2NR_2, nitro, and halo,wherein any C_1-C_6 alkyl, and C_3-C_6 cycloalkyl is optionally substituted with one or more groups independently selected from halo, cyano, hydroxy, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_3-C_6 cycloalkyl, and phenyl;

$\mathbf{Z}$ is selected from $-N(R^{15})-$, $-O-$, $-S-$, $-S(O)-$, and $-S(O)_2-$;

$\mathbf{R^{15}}$ is pyridyl that is substituted with $-(X^{15R})_{0\text{-}1}OR^{R15a}$ or $-(X^{15R})_{0\text{-}1}SR^{R15a}$, wherein X^{15R} is $C_{1\text{-}4}$ alkylene; wherein R^{R15a} is hydrogen, $C_{1\text{-}8}$ alkyl, $C_{2\text{-}8}$ alkenyl, $C_{1\text{-}8}$ haloalkyl, $C_{3\text{-}8}$ cycloalkyl, ($C_{3\text{-}8}$ cycloalkyl)$C_{1\text{-}8}$ alkyl, phenyl, (aryl)$C_{1\text{-}8}$ alkyl, and $C_{2\text{-}11}$ heterocycloalkyl; where any $C_{2\text{-}8}$ alkenyl, $C_{3\text{-}8}$ cycloalkyl, ($C_{3\text{-}8}$ cycloalkyl)$C_{1\text{-}8}$ alkyl, phenyl, (aryl)$C_{1\text{-}8}$ alkyl, and $C_{2\text{-}11}$ heterocycloalkyl of R^{R15a} is optionally substituted with from 1 to 5 substituents independently selected from the group consisting of $C_{1\text{-}8}$ haloalkyl, F, Cl, Br, I, -OH, -CN, and $-NO_2$;

X is selected from hydrogen, C_{1-8}alkyl, $-N(R^{16})_2$ and $-N(R^{17})_3^+$ ^-W, and amine oxides thereof;

$\mathbf{Y^1}$ is $-C(R^{18})_2-$; and $\mathbf{Y^2}$ is selected from $-(C(R^{18})_2)_n-$, $-N(R^{19})-$, $-O-$, $-C(R^{18})_2-N(R^{19})-$, $-N(R^{19})-C(R^{18})_2-$, $-C(R^{18})_2-O-$, and $-O-C(R^{18})_2-$; or

$\mathbf{Y^1}$ is selected from $-N(R^{19})-$ and $-O-$; and $\mathbf{Y^2}$ is $-(C(R^{18})_2)_n-$;

n is selected from 0, 1, and 2;

$\mathbf{Y^3}$ and $\mathbf{Y^6}$ are each $-C(R^{18})_2-$;

$\mathbf{Y^4}$ and $\mathbf{Y^5}$ are each $-C(R^{18})-$;

each $\mathbf{R^{16}}$ is independently selected from hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkanoyl, 4-7 membered heterocycle, 5-6 membered heteroaryl, and C_6-C_{12} aryl, wherein any C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkanoyl, 4-7 membered heterocycle, 5-6 membered heteroaryl, and C_6-C_{12} aryl is optionally substituted with one or more groups independently selected from deuterium, halo, cyano, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkanoyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_3-C_6 cycloalkyl, C_3-C_6 halocycloalkyl, $-NR^aR^b$, $-C(=O)NR^aR^b$, R^c, and phenyl, wherein any C_1-C_6 alkyl, C_1-C_6 alkoxy, and C_1-C_6 alkanoyl is optionally substituted with C_3-C_6 cycloalkyl; or two R^{16} groups together with the nitrogen to which they are both attached form a 4- to 10-membered heterocycle that is optionally substituted with one or more groups independently selected from deuterium, halo, cyano, hydroxy, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl, which C_1-C_6 alkyl, and C_3-C_6 cycloalkyl is optionally substituted with one or more groups independently selected from hydroxy and halo;

each $\mathbf{R^{17}}$ is independently selected from C_1-C_6 alkyl; or two R^{17} groups together with the nitrogen to which they are both attached form a 4- to 7-membered heterocycle;

each $\mathbf{R^{18}}$ is independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_6 cycloalkyl, benzyl, 5-15 membered heteroaryl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_3-C_6 cycloalkoxy, hydroxy, halo, cyano, and $-L$-C_6-C_{12} aryl; wherein each C_3-C_6 cycloalkyl, -L-C_6-C_{12} aryl, benzyl, 5-15 membered heteroaryl, and C_1-C_6 alkoxy, is optionally substituted with one to three substituents R^x each independently selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, cyano, halo, hydroxy, C_3-C_6 cycloalkoxy, C_3-C_6 halocycloalkyl, -S(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -S(O)$_2$(C_1-C_6 alkyl), -NH_2 -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, 4-6 membered heterocycle, and C_1-C_6 haloalkyl or two R^{18} that are on adjacent carbons taken together form a double bond; and

R^{19} is selected from hydrogen, C_1-C_6 alkyl and C_6-C_{12} aryl, which C_6-C_{12} aryl is optionally substituted with one to three substituents each independently selected from C_1-C_6 alkyl,

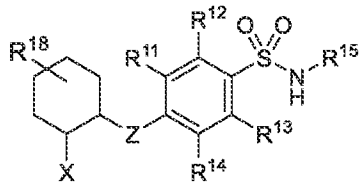
C_3-C_6 cycloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, cyano, halo, and C_1-C_6 haloalkyl; or one R^{18} or R^{19} taken together with another R^{18} or R^{19} and the atoms to which they are attached form a 3-8 membered fused, bridged or spirocyclic ring, which 3-8 membered ring is optionally substituted with one to three substituents each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, cyano, halo, and C_1-C_6 haloalkyl; and L is selected from a bond, −O−, −S−, −S(O)−, and −$S(O)_2$−;

each $\mathbf{R^a}$ and $\mathbf{R^b}$ is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_1-C_6 alkanoyl;

each $\mathbf{R^c}$ is independently selected from 4-7 membered heterocycle that is optionally substituted with one or more groups independently selected from halo, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; and

$\mathbf{W^-}$ is a counterion.

17. The compound of claim 17, which is a compound of formula IIa:



IIa

or a pharmaceutically acceptable salt thereof.

18. The compound or pharmaceutically acceptable salt of any one of claims 16 or 17, wherein X is −$N(R^{16})_2$ and each R^{16} is independently selected from hydrogen, C_2-C_6 alkoxyalkyl, C_1-C_6 alkyl, benzyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, and C_1-C_6 hydroxyalkyl; or a pharmaceutically acceptable salt thereof.

19. The compound or pharmaceutically acceptable salt of any one of claims 16 or 17, wherein X is dimethylamino.

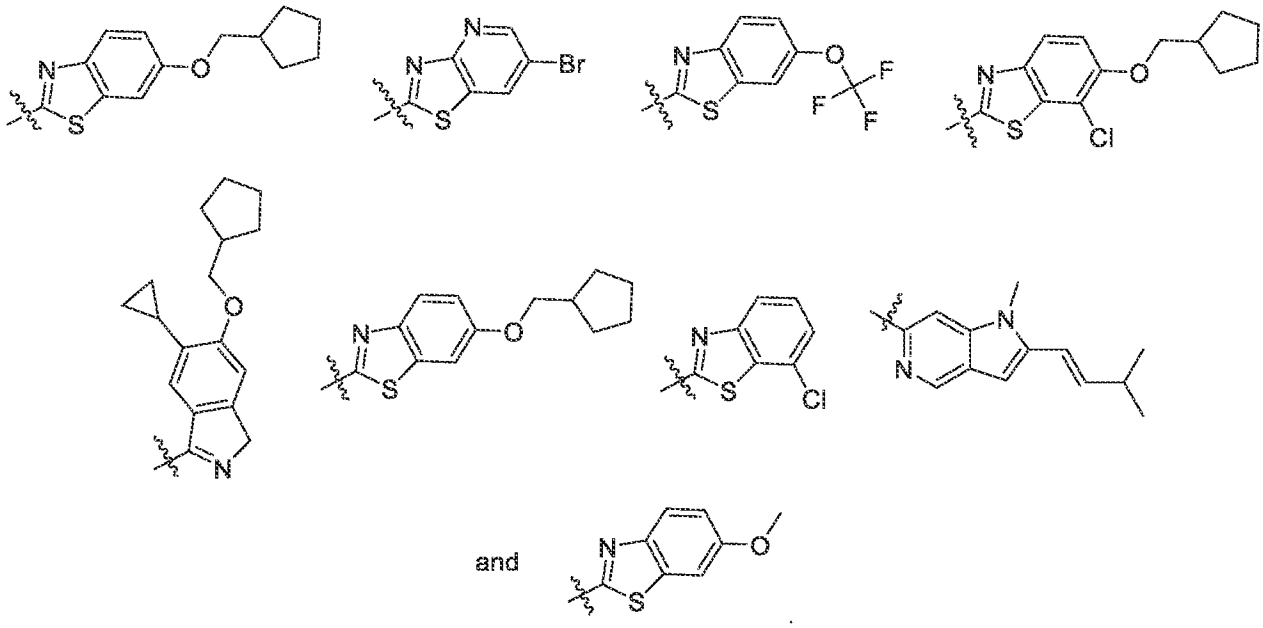
20. The compound or pharmaceutically acceptable salt of any one of claims 16 – 19, wherein R^{11} is H or F, or a pharmaceutically acceptable salt thereof.

21. The compound or pharmaceutically acceptable salt of any one of claims 16 – 20, wherein R^{12} is hydrogen, or a pharmaceutically acceptable salt thereof.

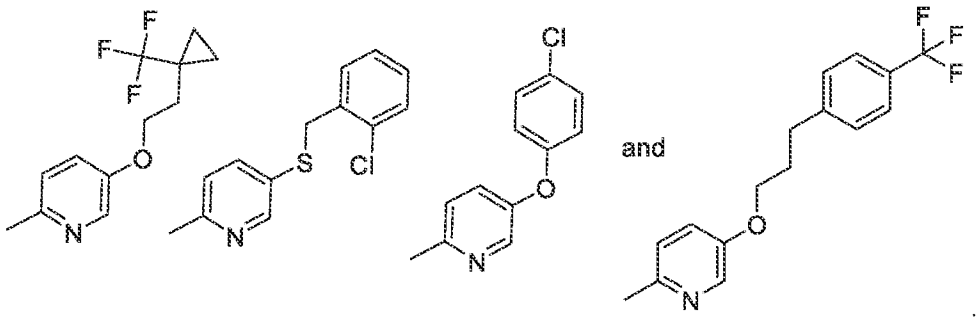
22. The compound or pharmaceutically acceptable salt of any one of claims 16 – 21, wherein R^{13} is selected from hydrogen and fluoro; or a pharmaceutically acceptable salt thereof.

23. The compound or pharmaceutically acceptable salt of any one of claims 16 – 22, wherein R^{14} is hydrogen; or a pharmaceutically acceptable salt thereof.

24. The compound or pharmaceutically acceptable salt of any one of claims 16 – 23, wherein R^{15} is selected from the group consisting of:



25. The compound or pharmaceutically acceptable salt of any one of claims 16 – 23, wherein R^{15} is selected from the group consisting of:



26. The compound or pharmaceutically acceptable salt of claim 16, which is selected from the group consisting of:

Ex. 95: N-(6-bromothiazolo[4,5-b]pyridin-2-yl)-4-(((1S,2S)-2-(dimethylamino)-cyclohexyl)amino)-2-fluorobenzenesulfonamide;

Ex. 96: N-(6-(cyclopentylmethoxy)benzo[d]thiazol-2-yl)-4-(((1S,2S)-2-(dimethyl-amino)cyclohexyl)-amino)-2-fluorobenzenesulfonamide;

Ex. 97: N-(6-(cyclopentylmethoxy)benzo[d]thiazol-2-yl)-4-(((1S,2S)-2-(dimethyl-amino)cyclohexyl)oxy)-2-fluorobenzenesulfonamide;

Ex. 99: N-(7-chlorobenzo[d]thiazol-2-yl)-4-(((1S,2S)-2-(dimethylamino)cyclo-hexyl)-oxy)-2-fluorobenzenesulfonamide;

Ex. 101: 5-chloro-4-(((1S,2S)-2-(dimethylamino)cyclohexyl)amino)-2-fluoro-N-(5-(2-(1-(trifluoromethyl)cyclopropyl)ethoxy)pyridin-2-yl)benzenesulfonamide;

Ex. 102: 5-chloro-4-(((1S,2S)-2-(dimethylamino)cyclohexyl)amino)-2-fluoro-N-(1-methyl-2-((E)-3-methylbut-1-en-1-yl)-1H-pyrrolo[3,2-c]pyridin-6-yl)benzenesulfonamide;

Ex. 103: 5-chloro-4-(((1S,2S)-2-(dimethylamino)cyclohexyl)amino)-2-fluoro-N-(5-(3-(4-(trifluoromethyl)phenyl)propoxy)pyridin-2-yl) benzenesulfonamide;

Ex. 201: 4-(((1S,2S)-2-(dimethylamino)cyclohexyl)amino)-2-fluoro-N-(6-methoxybenzo[d]thiazol-2-yl)benzenesulfonamide;

Ex. 202: 5-chloro-N-(6-(cyclopentylmethoxy)benzo[d]thiazol-2-yl)-4-(((1S,2S)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzenesulfonamide;

Ex. 203: 4-(((1S,2S)-2-(dimethylamino)cyclohexyl)amino)-2-fluoro-N-(6-(trifluoromethoxy)benzo[d]thiazol-2-yl)benzenesulfonamide;

Ex. 257: N-(5-((2-chlorobenzyl)thio)pyridin-2-yl)-4-(((1S,2S)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzenesulfonamide;

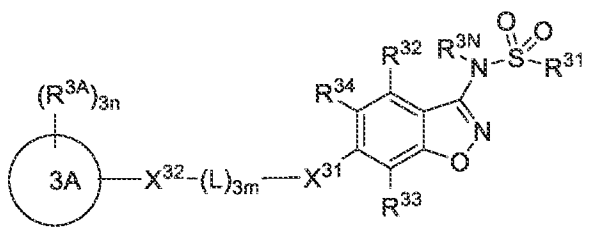
Ex. 258: N-(5-(4-chlorophenoxy)pyridin-2-yl)-4-(((1S,2S)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzenesulfonamide;

Ex. 332: 4-(((1S,2S)-2-(dimethylamino)cyclohexyl)amino)-2-fluoro-N-(thiazol-2-yl)benzenesulfonamide; and

Ex. 333: N-(7-chloro-6-(cyclopentylmethoxy)benzo[d]thiazol-2-yl)-4-(((1S,2S)-2-(dimethylamino)cyclohexyl)amino)-2-fluorobenzenesulfonamide,

or pharmaceutically acceptable salts thereof.

27. A compound of Formula III:



III

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{R^{31}}$ is selected from a first set of moieties consisting of C_{1-8}alkyl, C_{3-12}cycloalkyl, C-linked C_{2-11}heterocycloalkyl, C_{3-12}carbocycle, aryl, heteroaryl, and $-NR^{31A}R^{31B}$, wherein:

R^{31A} and R^{31B} are selected from H, C_{1-8}alkyl, C_{3-8}cycloalkyl, C_{1-8}haloalkyl, or R^{31A} and R^{31B} together with the nitrogen atom to which they are both bonded form a 3 to 10 membered heterocyclic group;

any of the first set of moieties, R^{31A}, or R^{31B}, is optionally substituted with one or more substituents selected from a second set of moieties consisting of:

C_{1-8}alkyl, C_{2-8}alkenyl, C_{3-8}cycloalkyl, C_{1-8}haloalkyl, aryl, (aryl)C_{1-8}alkyl, heteroaryl, (heteroaryl)C_{1-8}alkyl, C_{2-11}heterocycloalkyl, (C_{2-11}heterocycloalkyl)C_{1-8}alkyl, F, Cl, Br, I, –OH, –CN, $-NO_2$, =O, aminocarbonyl, $-X^{R1}NR^{R1a}R^{R1b}$, $-X^{R1}OR^{R1a}$, and $-X^{R1}SR^{R1a}$, wherein:

X^{R1} is selected from the group consisting of C(=O), C_{1-4} alkylene, C_{1-4}heteroalkylene, C_{2-4}alkenylene and C_{2-4} alkynylene, or is absent; and

R^{R1a} and R^{R1b} are independently selected from a third set of moieties consisting of: H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{1-8}haloalkyl, C_{3-8}cycloalkyl, C_{3-12}carbocycle, (C_{3-8} cycloalkyl)C_{1-8} alkyl, aryl, (aryl)C_{1-8}alkyl, heteroaryl, (heteroaryl)C_{1-8}alkyl, C_{2-11}heterocycloalkyl, and (C_{2-11}heterocycloalkyl)C_{1-8}alkyl,

or R^{R1a} and R^{R1b} together with the nitrogen atom to which they are both bonded form a 3 to 10 membered heterocyclic group;

and

wherein any of the second set of moieties, R^{R1a}, or R^{R1b}, where present, are each optionally substituted by one or more groups independently selected from: C_{1-8} alkyl, C_{1-8}haloalkyl, F, Cl, Br, I, -OH, -CN, aryl, C_{1-8}haloalkyl-substituted aryl, C_{1-8}alkoxy, C_{1-8}alkanoyl, C_{1-8}alkoxycarbonyl, C_{3-8}cycloalkyl, C_{2-11}heterocycloalkyl, amino, (C_{1-3}alkyl)amino, di(C_{1-3}alkyl)amino, C_{1-3}alkylamido, C_{1-3}alkylcarboxy, and $-NO_2$;

$\mathbf{R^{3N}}$ is hydrogen, C_{1-4} alkyl or C_{1-4} haloalkyl;

$\mathbf{R^{32}}$ and $\mathbf{R^{33}}$ are independently selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{1-8} haloalkyl and C_{1-8} alkoxy;

$\mathbf{R^{34}}$ is selected from the group consisting of H, F, Cl, Br, I, -CN, C_{1-8} alkyl, C_{2-8} alkenyl, C_{1-8}haloalkyl, C_{1-8} alkoxy, C_{3-8} cycloalkyl, C_{2-11} heterocycloalkyl, phenyl and 5-6 membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O and S, wherein said 5-6 membered heteroaryl, C_{1-8} alkyl, C_{3-8} cycloalkyl or C_{2-11} heterocycloalkyl is

further optionally substituted with from 1 to 3 R^{5a} substituents selected from F, Cl, Br, I, -OH, =O, C_{3-6} cycloalkyl, -CN, C_{1-4} alkyl, -C_{1-4} alkyl-O-C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} alkoxy;

L is a linker selected from the group consisting of C_{1-4} alkylene, C_{2-4} alkenylene, C_{2-4} alkynylene, and C_{1-4} heteroalkylene, wherein L is optionally substituted with from 1 to 3 R^{L} substituents selected from the group consisting of =O, -OH, -OCH_2-phenyl, C_{1-4} alkyl, C_{1-4} haloalkyl and C_{1-4} acyl;

3m is 0 or 1;

$\mathbf{X^{31}}$ and $\mathbf{X^{32}}$ are each independently selected from the group consisting of absent, –O-, -S(O)-, -$S(O)_2$- and -$N(R^X)$- wherein R^x is H, C_{1-8} alkyl, C_{1-8} acyl or -$S(O)_2$(C_{1-8} alkyl), and wherein if 3m is 0 then at least one of X^1 or X^2 is absent;

3n is an integer from 0 to 5;

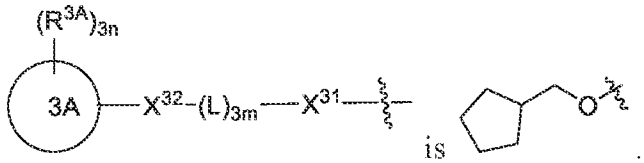
3A is selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8}haloalkyl, C_{3-12} cycloalkyl, and aryl, and wherein if 3A is hydrogen then n is 0; and

each $\mathbf{R^{3A}}$ is independently selected from the group consisting of C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-8} haloalkyl, F, Cl, Br, I, -OH, -CN, -NO_2, and =O.

28. The compound or pharmaceutically acceptable salt of claim 27, wherein $\mathbf{X^{31}}$ is -O-, and $\mathbf{X^{32}}$ is absent.

29. The compound or pharmaceutically acceptable salt of any one of claims 27 or 28, wherein **L** is methylene.

30. The compound or pharmaceutically acceptable salt of claim 27, wherein the group



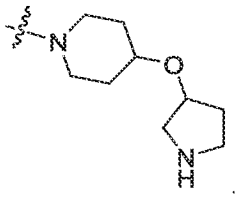
is .

31. The compound or pharmaceutically acceptable salt of any one of claims 27 – 30, wherein $\mathbf{R^{32}}$ and $\mathbf{R^{33}}$ are both H.

32. The compound or pharmaceutically acceptable salt of any one of claims 27 – 31, wherein $\mathbf{R^{34}}$ is selected from the group consisting of Cl and cyclopropyl.

33. The compound or pharmaceutically acceptable salt of any one of claims 27 – 32, wherein $\mathbf{R}^{3N}$ is hydrogen.

34. The compound or pharmaceutically acceptable salt of any one of claims 27 – 33, wherein $\mathbf{R}^{31}$ is:



35. The compound or pharmaceutically acceptable salt of claim 27, which is selected from the group consisting of:

Ex. 89: N-(6-(cyclopentylmethoxy)-5-cyclopropylbenzo[d]isoxazol-3-yl)-4-(((1S,2S)-2-(dimethylamino)cyclohexyl)oxy)-2-fluorobenzenesulfonamide;

Ex. 90: (R)-N-(5-chloro-6-(cyclopentylmethoxy)benzo[d]isoxazol-3-yl)-4-(pyrrolidin-3-yloxy)piperidine-1-sulfonamide;

Ex. 91: (S)-N-(6-(cyclopentylmethoxy)-5-cyclopropylbenzo[d]isoxazol-3-yl)-4-(pyrrolidin-3-yloxy)piperidine-1-sulfonamide 2,2,2-trifluoroacetate;

Ex. 92: (R)-N-(6-(cyclopentylmethoxy)-5-cyclopropylbenzo[d]isoxazol-3-yl)-4-(pyrrolidin-3-yloxy)piperidine-1-sulfonamide;

Ex. 93: (4aR,8aR)-N-(5-cyclopropylbenzo[d]isoxazol-3-yl)-1-(2-fluoro-5-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-2-oxohexahydro-1H-pyrido[3,4-b][1,4]oxazine-6(7H)-sulfonamide; and

Ex. 94: (4aS,8aS)-N-(5-cyclopropylbenzo[d]isoxazol-3-yl)-1-(2-fluoro-5-methoxy-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-2-oxohexahydro-1H-pyrido[3,4-b][1,4]oxazine-6(7H)-sulfonamide;

or pharmaceutically acceptable salts thereof.

36. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt as described in any one of claims 1 – 35 and a pharmaceutically acceptable excipient.

37. A method of treating a disease or condition in a mammal selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, and combinations thereof, wherein the method comprises administering to the mammal

in need thereof a therapeutically effective amount of a compound or a pharmaceutically acceptable salt as described in any one of claims 1 – 35.

38. The method of claim 37, wherein said disease or condition is selected from the group consisting of neuropathic pain, inflammatory pain, visceral pain, cancer pain, chemotherapy pain, trauma pain, surgical pain, post-surgical pain, childbirth pain, labor pain, neurogenic bladder, ulcerative colitis, chronic pain, persistent pain, peripherally mediated pain, centrally mediated pain, chronic headache, migraine headache, sinus headache, tension headache, phantom limb pain, dental pain, peripheral nerve injury or a combination thereof.

39. The method of claim 37, wherein said disease or condition is selected from the group consisting of pain associated with HIV, HIV treatment induced neuropathy, trigeminal neuralgia, post-herpetic neuralgia, eudynia, heat sensitivity, tosarcoidosis, irritable bowel syndrome, Crohns disease, pain associated with multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), diabetic neuropathy, peripheral neuropathy, arthritis, rheumatoid arthritis, osteoarthritis, atherosclerosis, paroxysmal dystonia, myasthenia syndromes, myotonia, malignant hyperthermia, cystic fibrosis, pseudoaldosteronism, rhabdomyolysis, hypothyroidism, bipolar depression, anxiety, schizophrenia, sodium channel toxi related illnesses, familial erythromelalgia, primary erythromelalgia, familial rectal pain, cancer, epilepsy, partial and general tonic seizures, restless leg syndrome, arrhythmias, fibromyalgia, neuroprotection under ischaemic conditions cause by stroke or neural trauma, tach-arrhythmias, atrial fibrillation and ventricular fibrillation.

40. A method of treating pruritus in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound or a pharmaceutically acceptable salt as described in any one of claims 1 – 35.

41. A compound or a pharmaceutically acceptable salt as described in any one of claims 1 – 35 for the use as a medicament for the treatment of diseases and disorders selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, or a combination thereof.

42. The use of a compound or a pharmaceutically acceptable salt as described in any one of claims 1 – 35 for the manufacture of a medicament for the treatment of diseases and disorders selected from the group consisting of pain, depression, cardiovascular diseases, respiratory diseases, and psychiatric diseases, or a combination thereof.

43. A compound or a pharmaceutically acceptable salt as described in any one of claims 1 – 35 for the prophylactic or therapeutic treatment of pain, depression, cardiovascular disease, respiratory disease, or psychiatric disease.

44. A compound or a pharmaceutically acceptable salt as described in any one of claims 1 – 35, for use in medical therapy.

45. A computer-based method of designing an inhibitor of NaV1.7, the method comprising docking molecular structures of compounds into a model of the NaV1.7 binding site based on coordinates found in the PDB File in Appendix 1.

46. A method of identifying a compound that binds to the VSD4 domain of the NaV1.7 receptor, the method comprising:

computationally modeling a test molecule that fits spatially into an atomic structural model of the NaV1.7 receptor VSD4 binding site or portion thereof, wherein said atomic structural model comprises atomic coordinates found in Appendix 1; and

screening said test molecule in an assay characterized by binding of the test molecule to the VSD4 binding site of the NaV1.7 receptor, thereby identifying a compound that inhibits NaV1.7 receptor activity..

47. The invention as hereinbefore described.

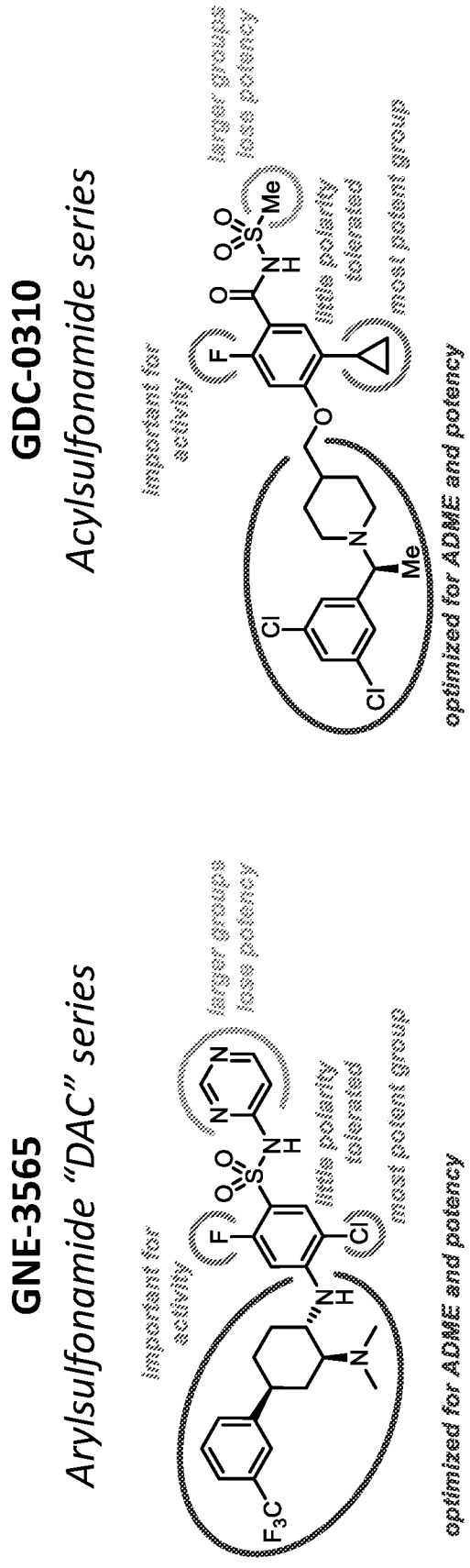

GDC-0310
Acylsulfonamide series
important for activity
larger groups lose potency
little polarity tolerated
most potent group
optimized for ADME and potency
GNE-3565
Arylsulfonamide "DAC" series
important for activity
larger groups lose potency
little polarity tolerated
most potent group
optimized for ADME and potency

FIG. 1

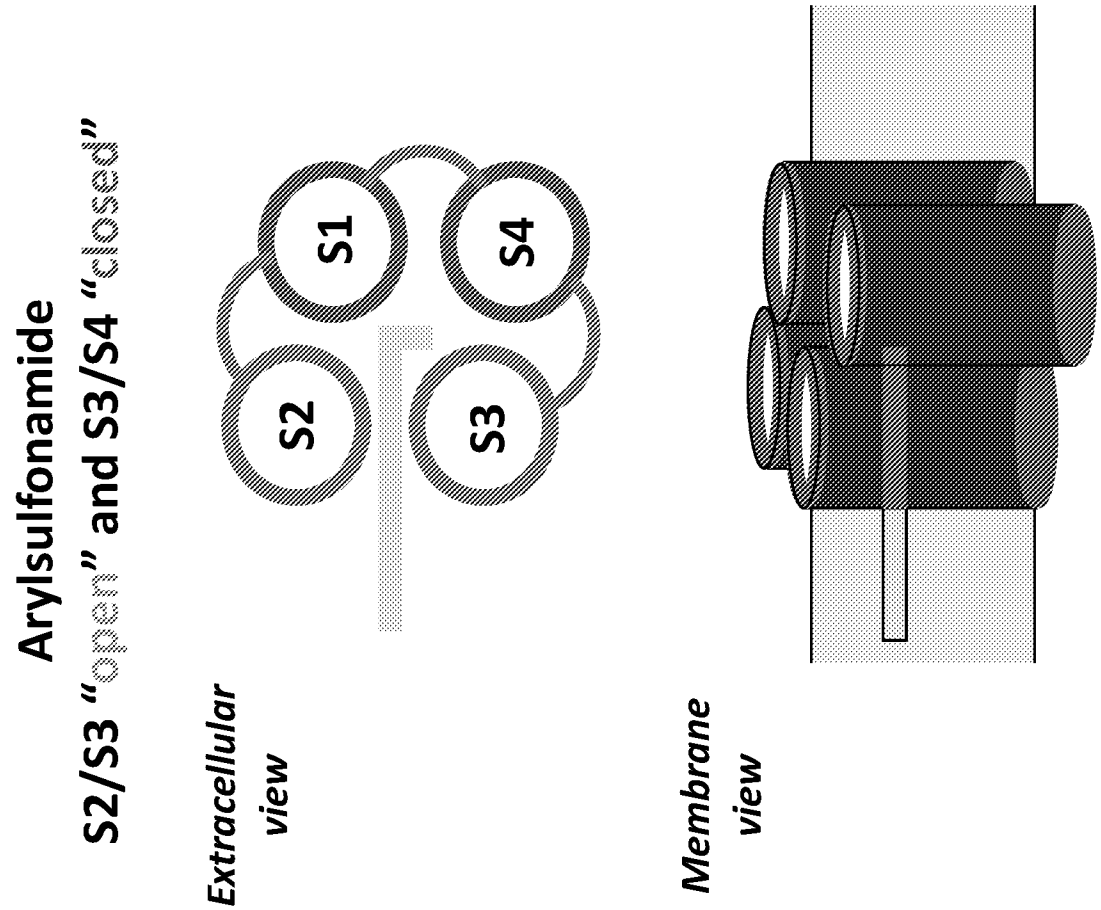

Arylsulfonamide
S2/S3 "open" and S3/S4 "closed"
Extracellular view
S1
S2
S3
S4
Membrane view

FIG. 2A

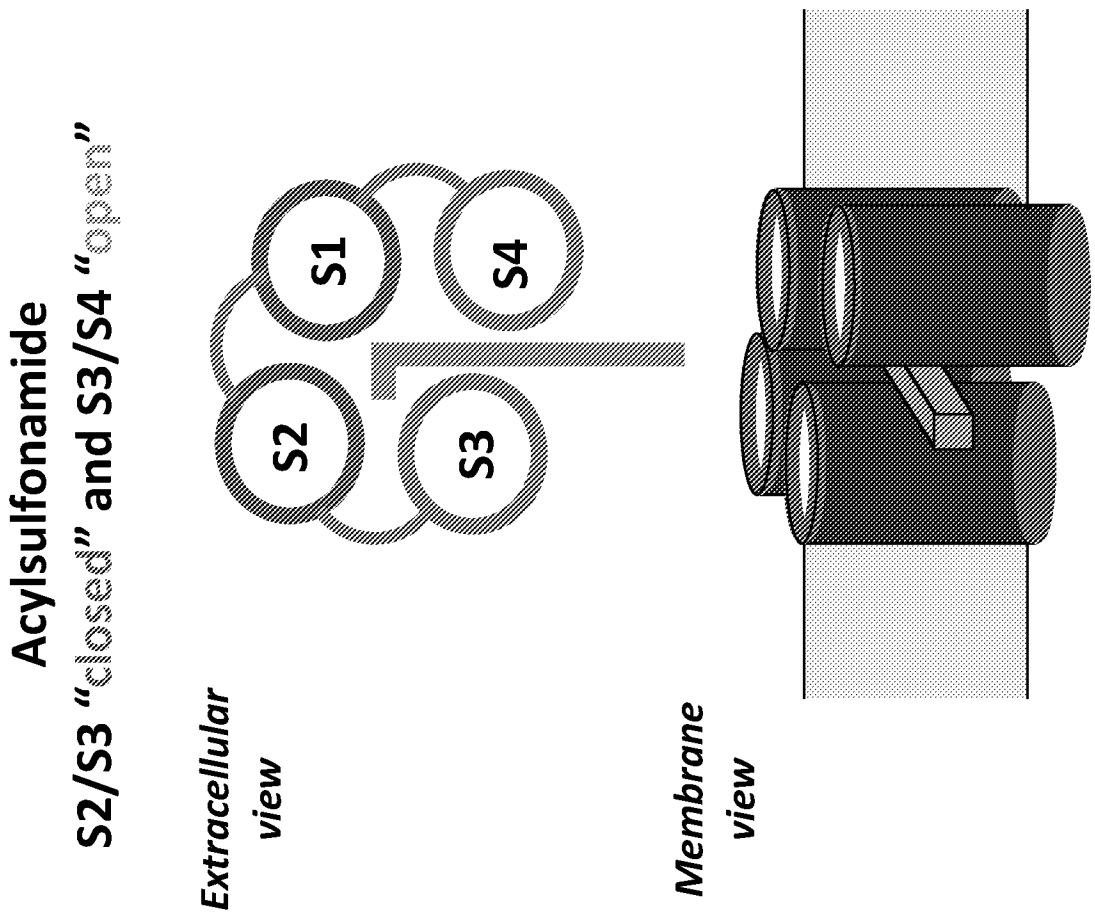

Acylsulfonamide
S2/S3 "closed" and S3/S4 "open"
Extracellular view
S1
S2
S3
S4
Membrane view

FIG. 2B

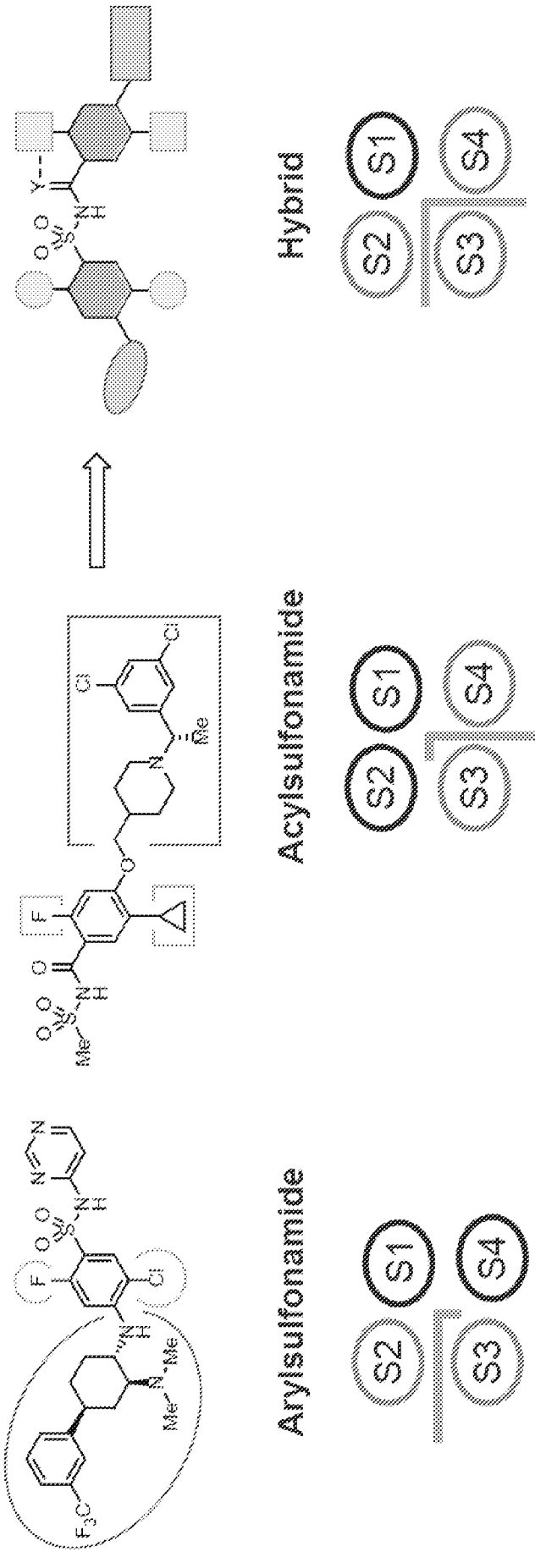

Arylsulfonamide
S1
S2
S3
S4
Acylsulfonamide
S1
S2
S3
S4
Hybrid
S1
S2
S3
S4

FIG. 3A

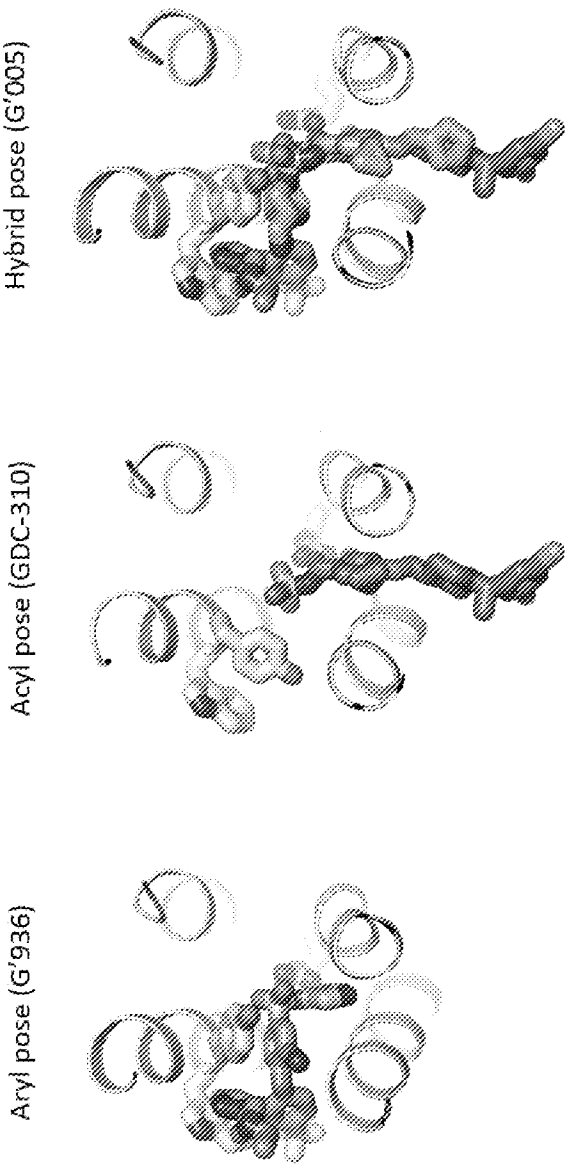

Aryl pose (G'936)
Acyl pose (GDC-310)
Hybrid pose (G'005)

FIG. 3B

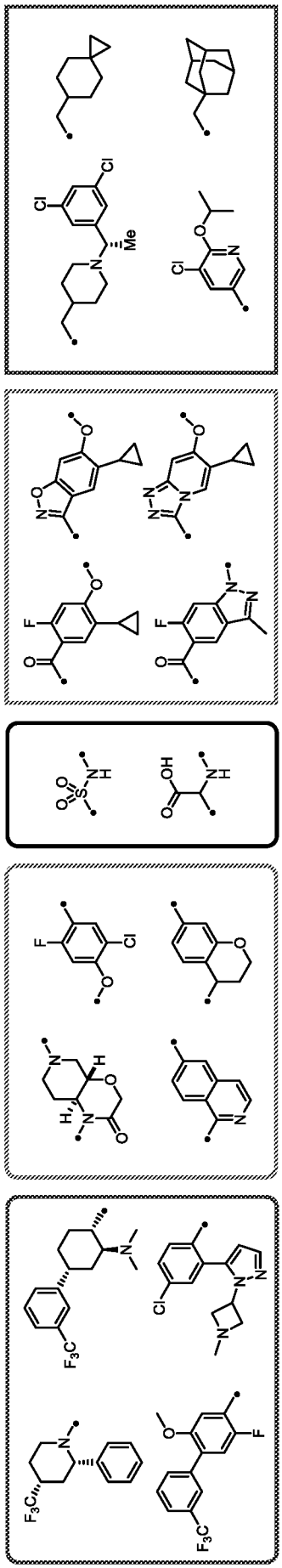
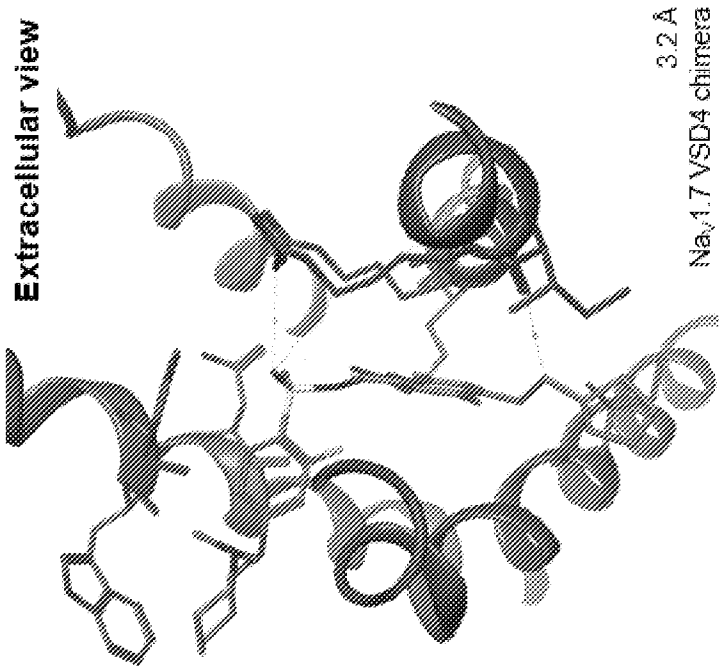

Aryl Tail
S2/S3 Ring
Warhead
S3/S4 Ring
Acyl Tail

FIG. 4


Extracellular view
3.2 Å
Na$_v$1.7 VSD4 chimera

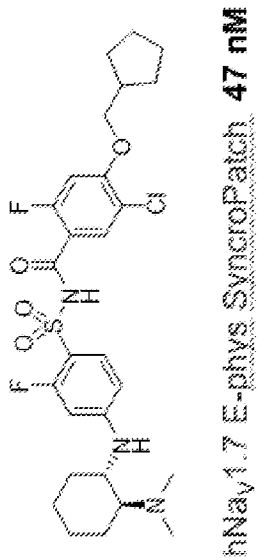
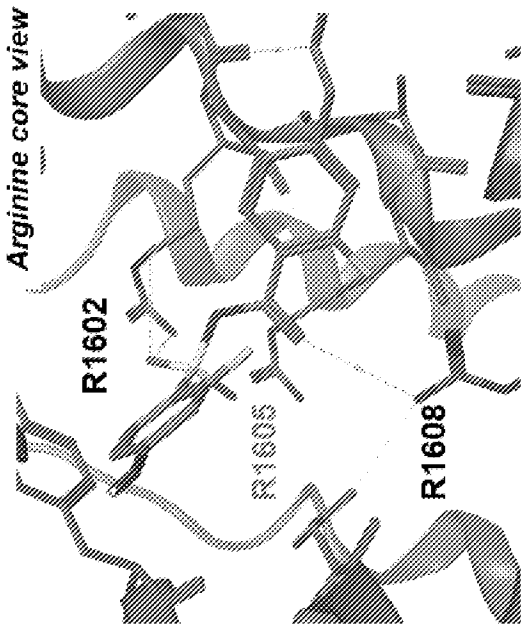
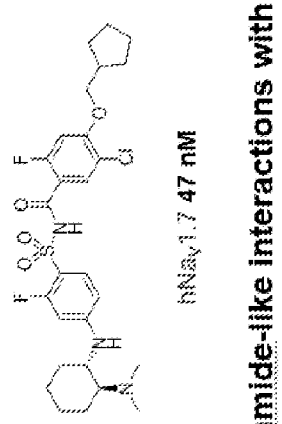

hNa$_v$1.7 E-phys SyncroPatch 47 nM

FIG. 5A

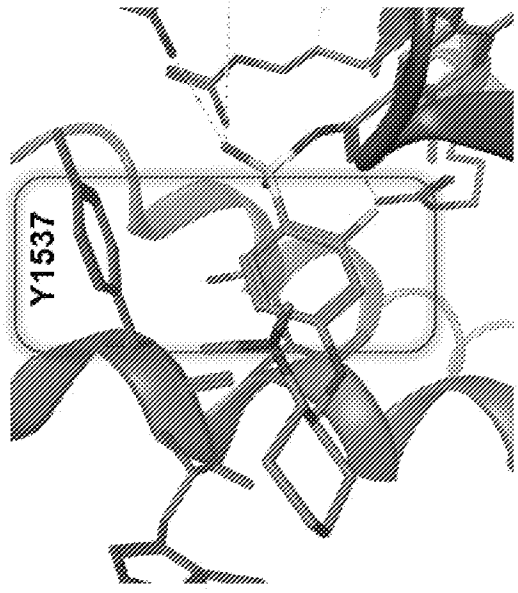


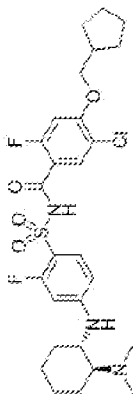


hNav1.7 47 nM

Arylsulfonamide-like interactions with R1608 and R1602

FIG. 5B





hNav1.7 47 nM

π-stacking with Y1537 lost

FIG. 5C

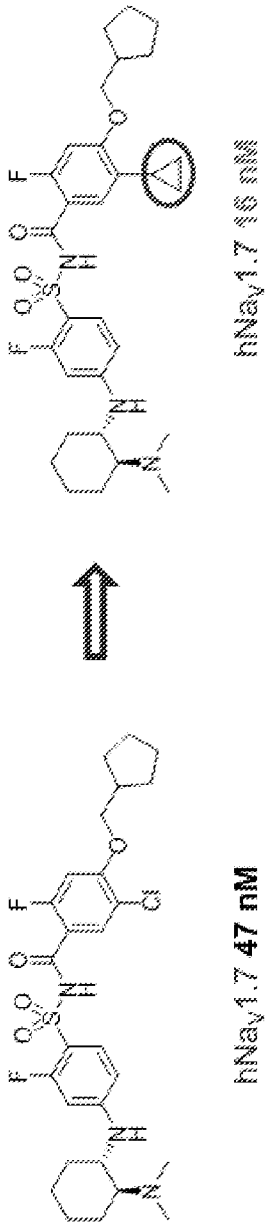

hNav1.7 47 nM
hNav1.7 16 nM

FIG. 6A

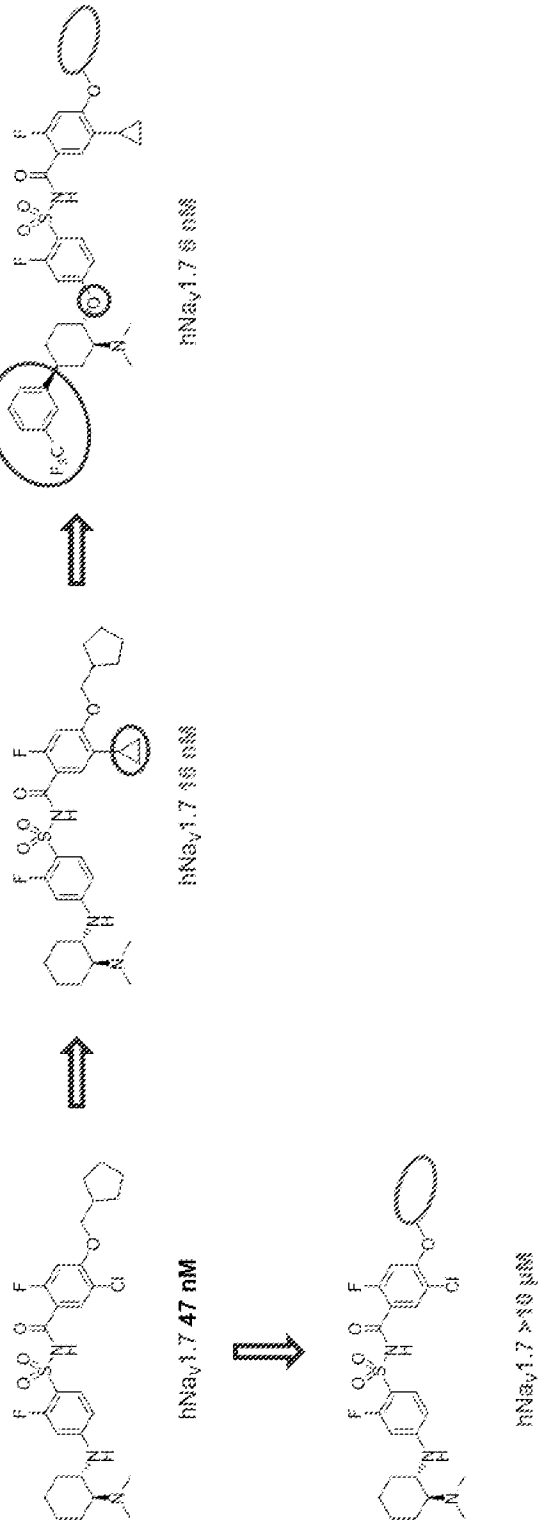

hNav1.7 47 nM
hNav1.7 16 nM
hNav1.7 8 nM
hNav1.7 >10 µM

FIG. 6B

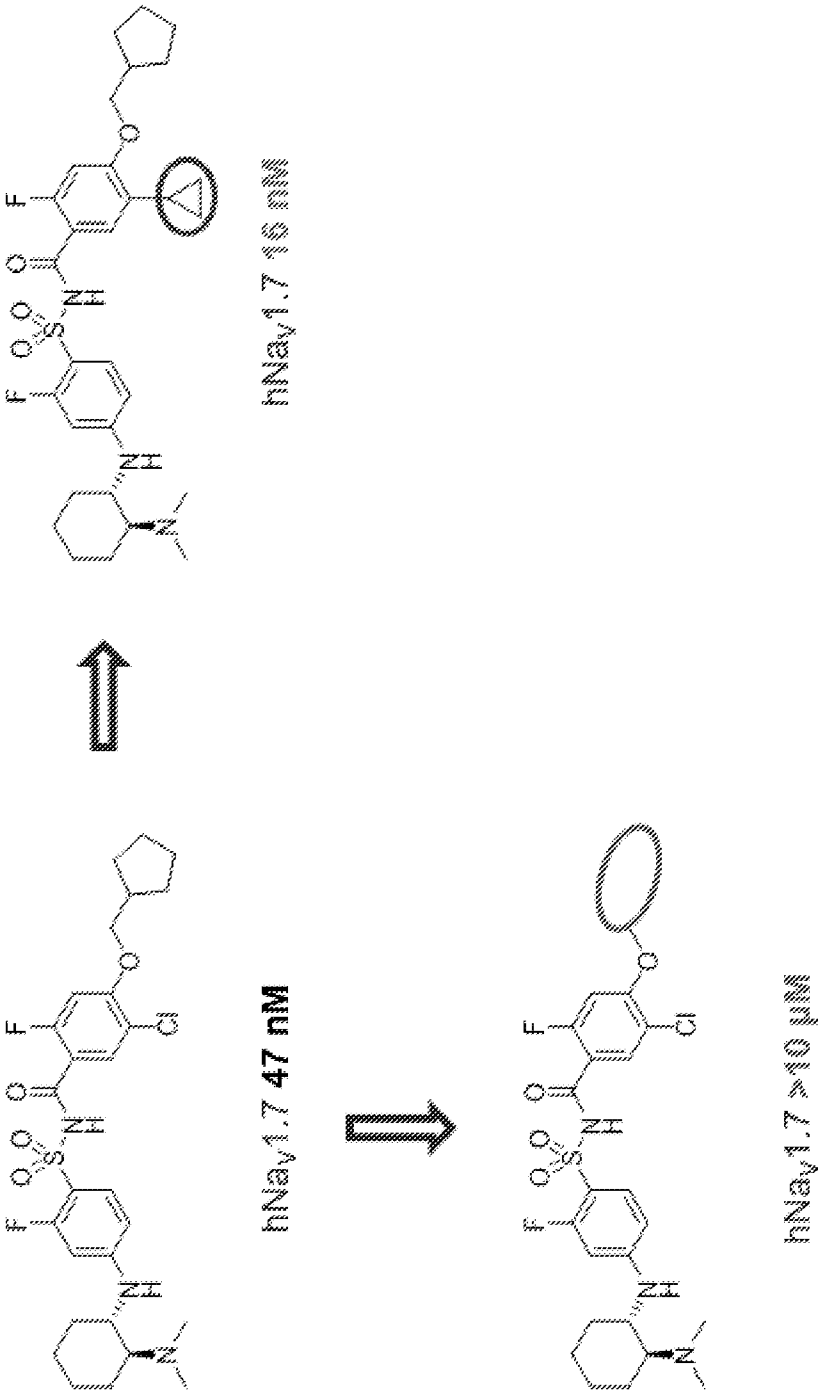


FIG. 6C

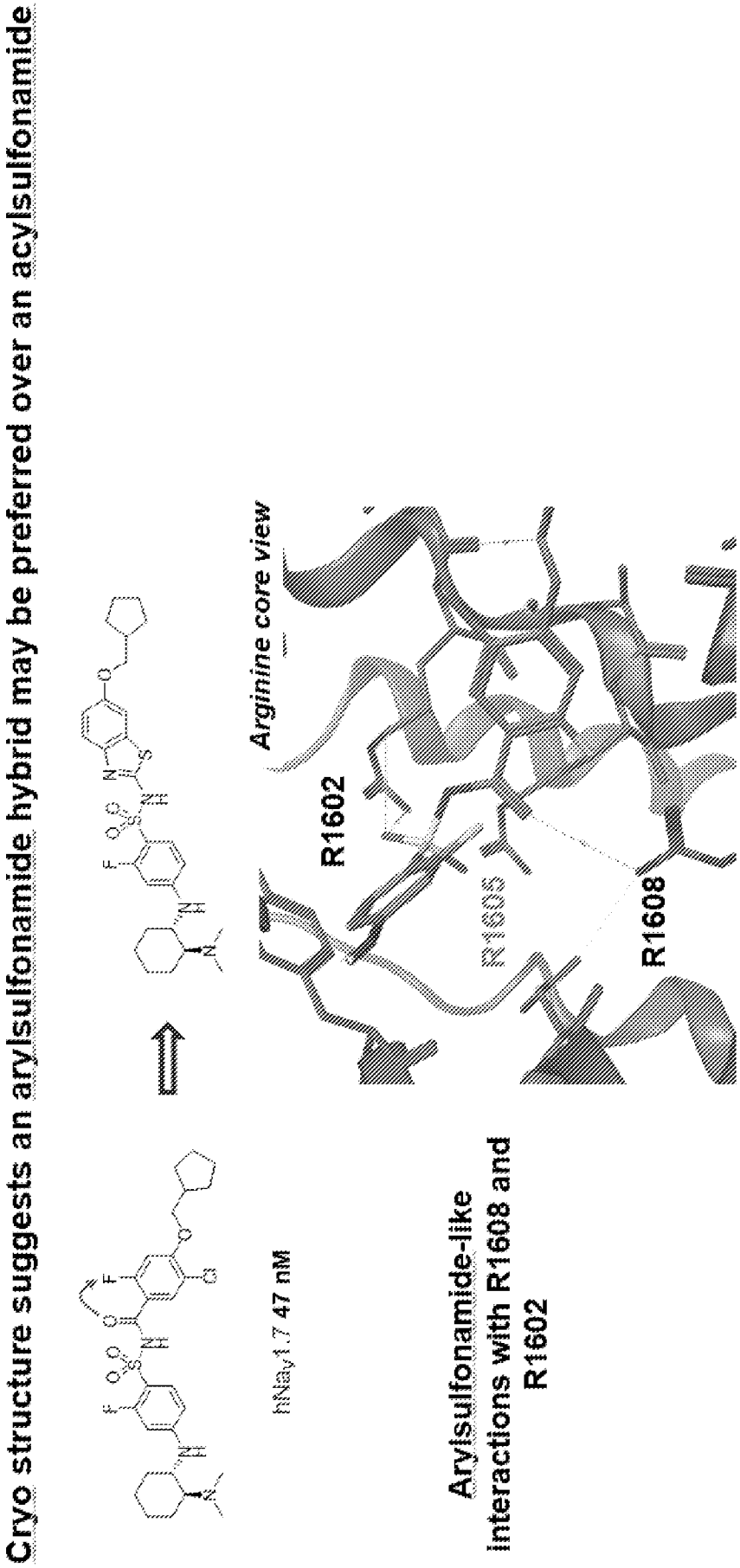
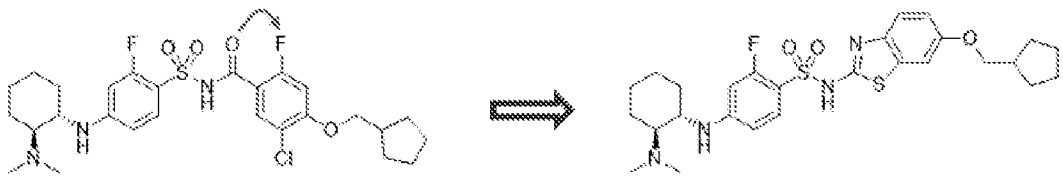

Cryo structure suggests an arylsulfonamide hybrid may be preferred over an acylsulfonamide
hNav1.7 47 nM
Arylsulfonamide-like interactions with R1608 and R1602
Arginine core view
R1602
R1605
R1608

FIG. 7A

Arylsulfonamide hybrid improves potency and affords high resolution structure

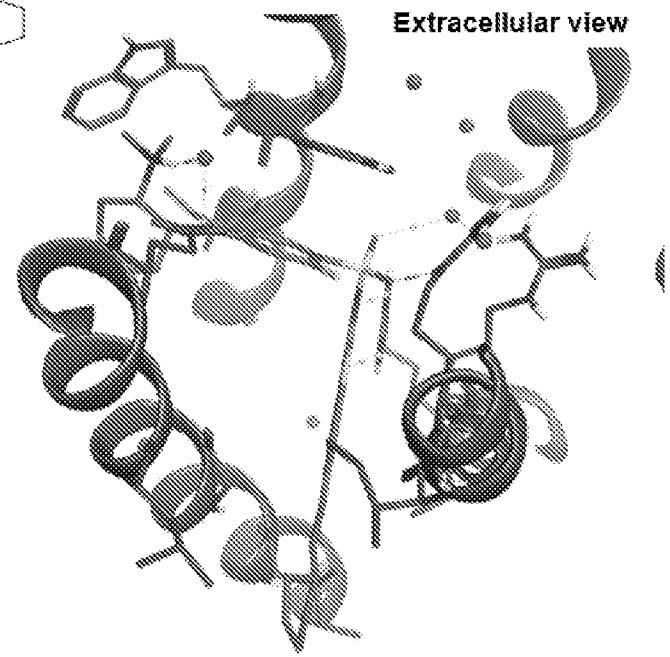


hNa$_V$1.7 **47 nM**

hNa$_V$1.7 8 nM

2.2 Å is the highest resolution structure reported for a sodium or calcium channel

Key water interactions visible for the first time



2.2 Å
Na$_V$1.7 VSD4 chimera

FIG. 7B

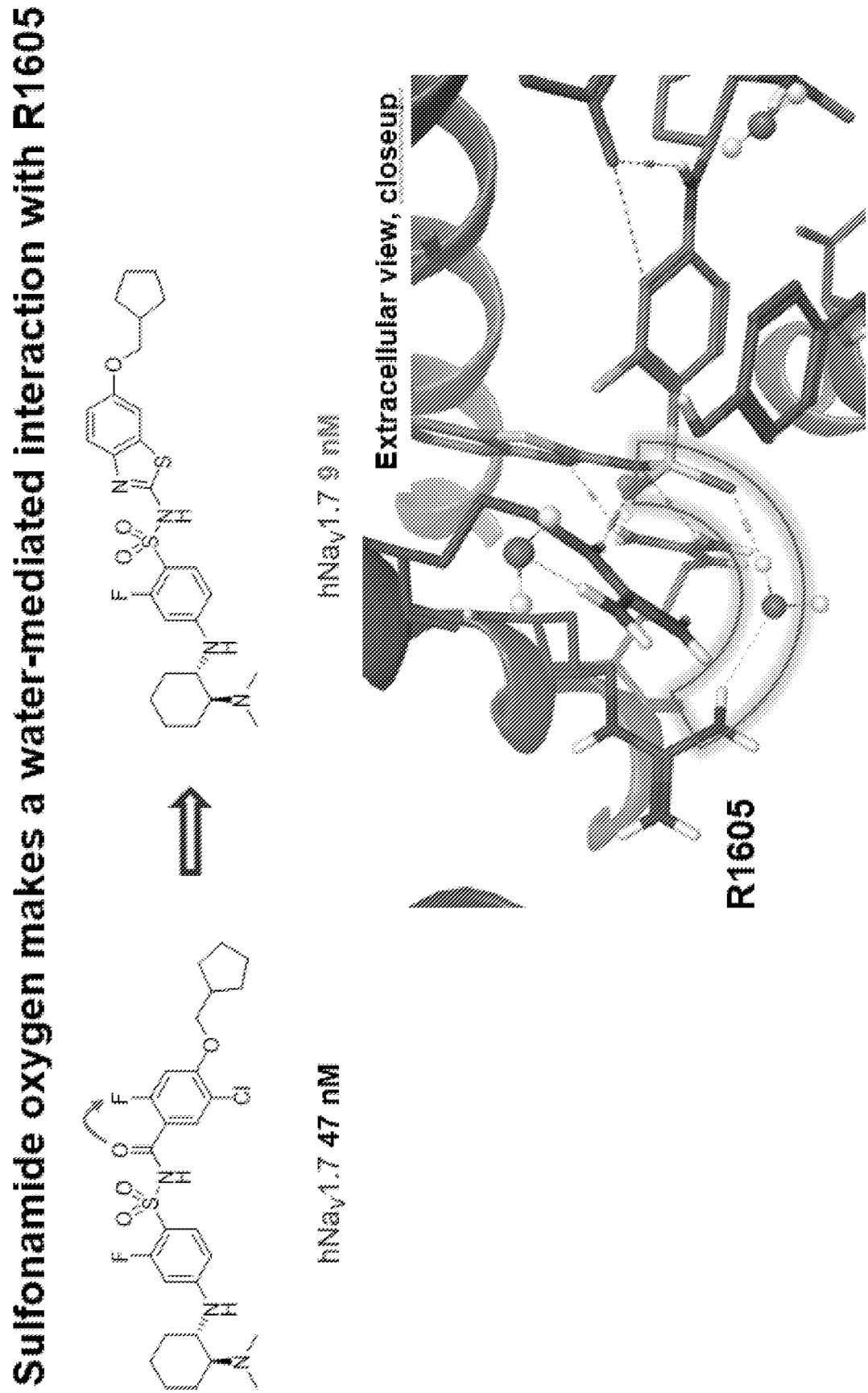

Sulfonamide oxygen makes a water-mediated interaction with R1605
hNav1.7 47 nM
hNav1.7 9 nM
Extracellular view, closeup
R1605

FIG. 7C

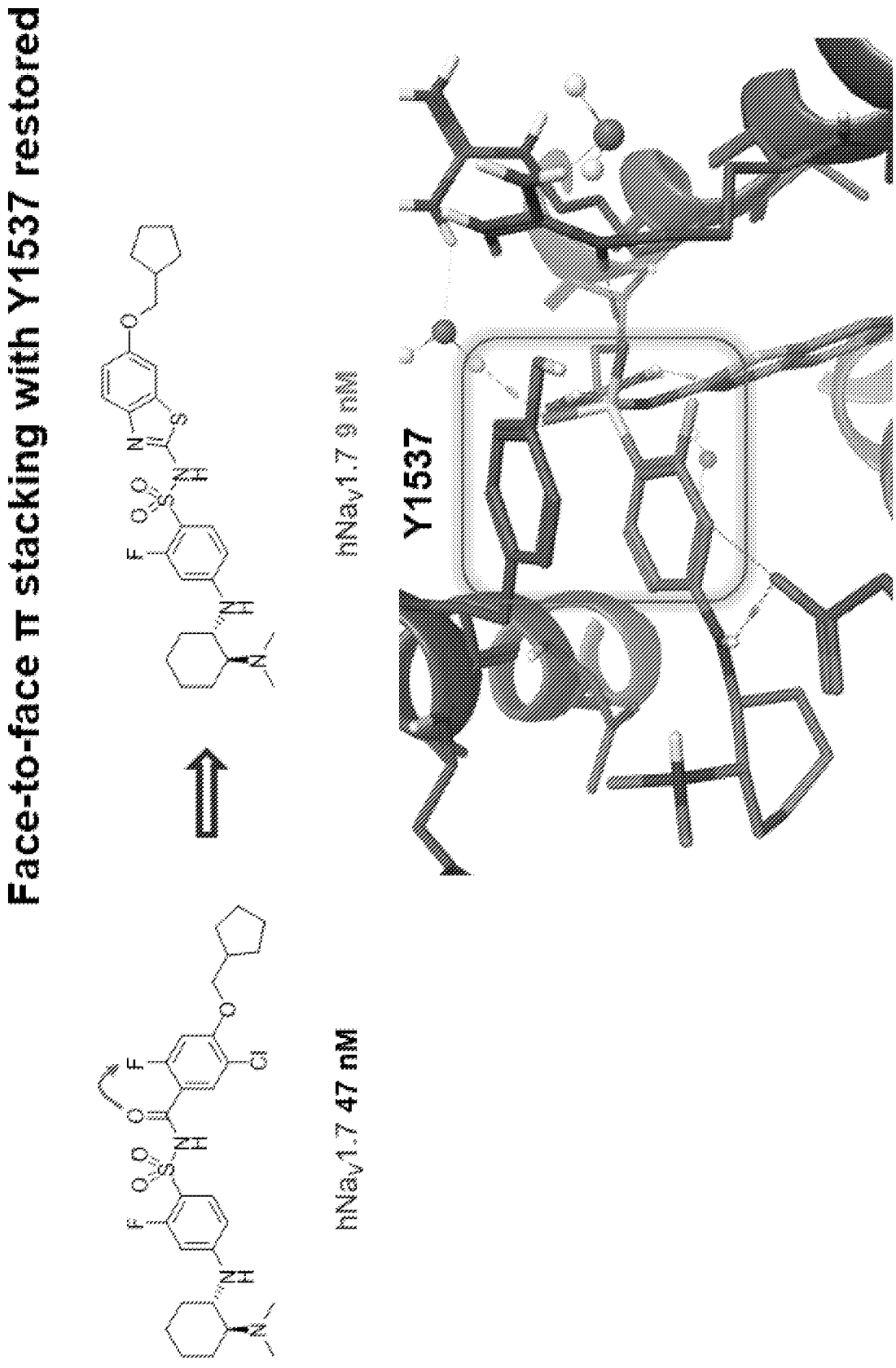

Face-to-face π stacking with Y1537 restored
hNav1.7 47 nM
hNav1.7 9 nM
Y1537

FIG. 7D

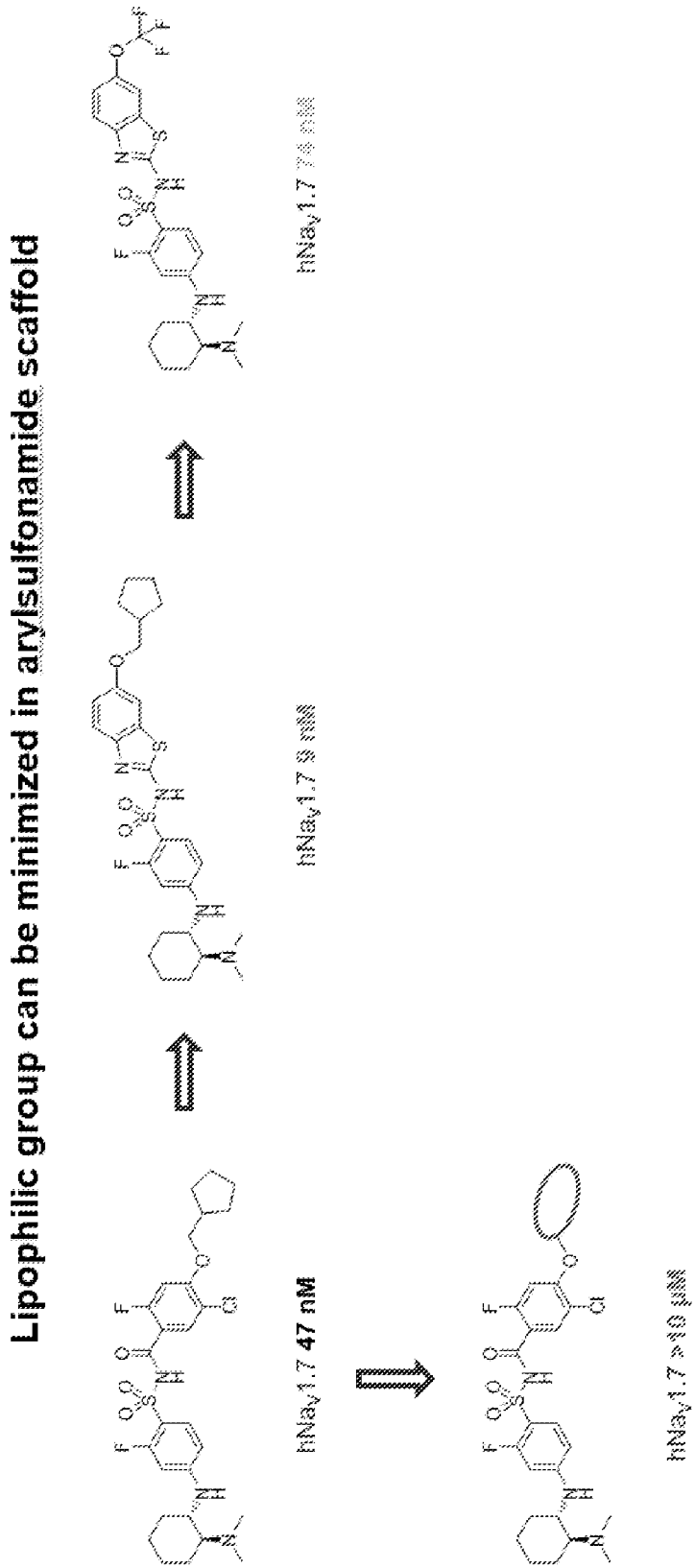

Lipophilic group can be minimized in arylsulfonamide scaffold
hNav1.7 47 nM
hNav1.7 9 nM
hNav1.7 78 nM
hNav1.7 >10 μM

FIG. 7E

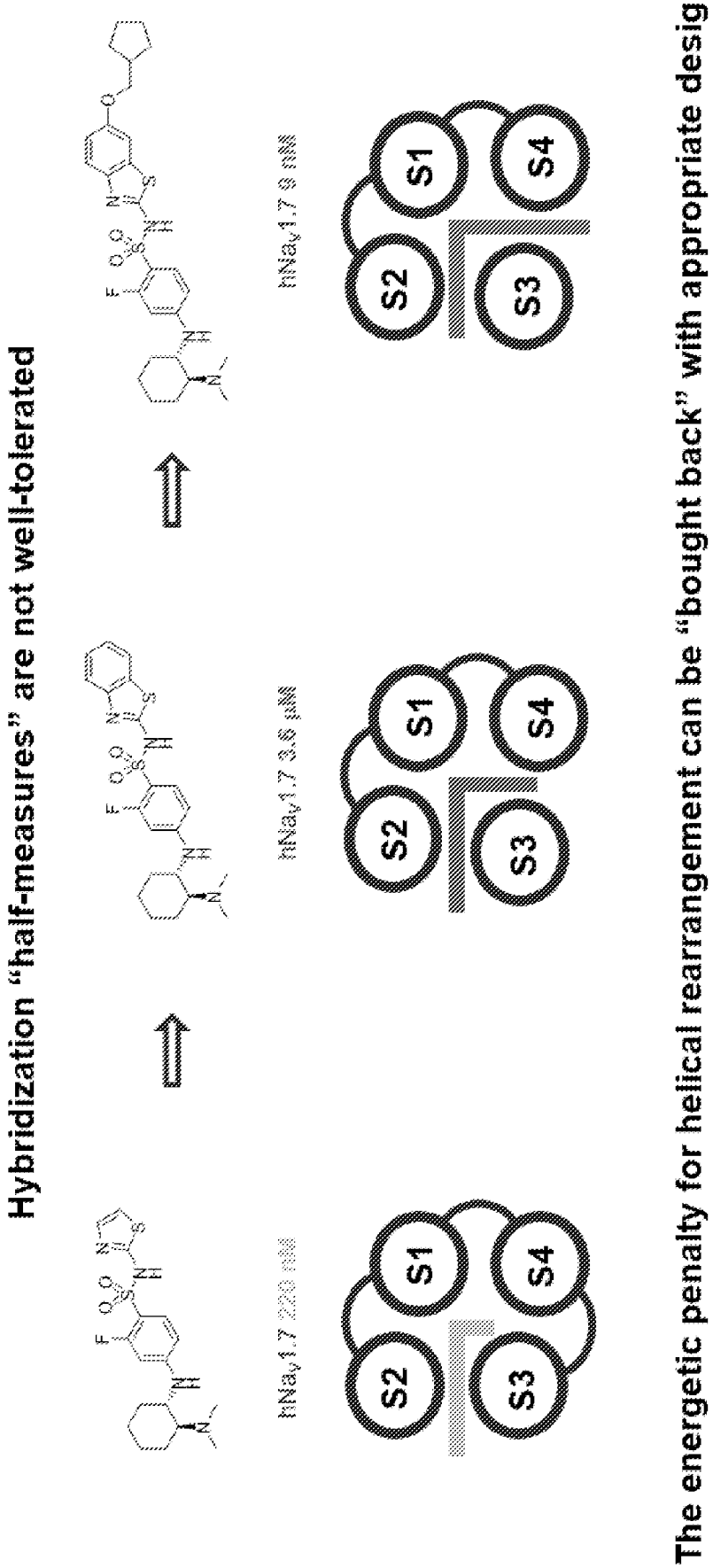

Hybridization "half-measures" are not well-tolerated
hNav1.7 220 nM
hNav1.7 3.6 μM
hNav1.7 8 nM
S1
S2
S3
S4
The energetic penalty for helical rearrangement can be "bought back" with appropriate design

FIG. 8A

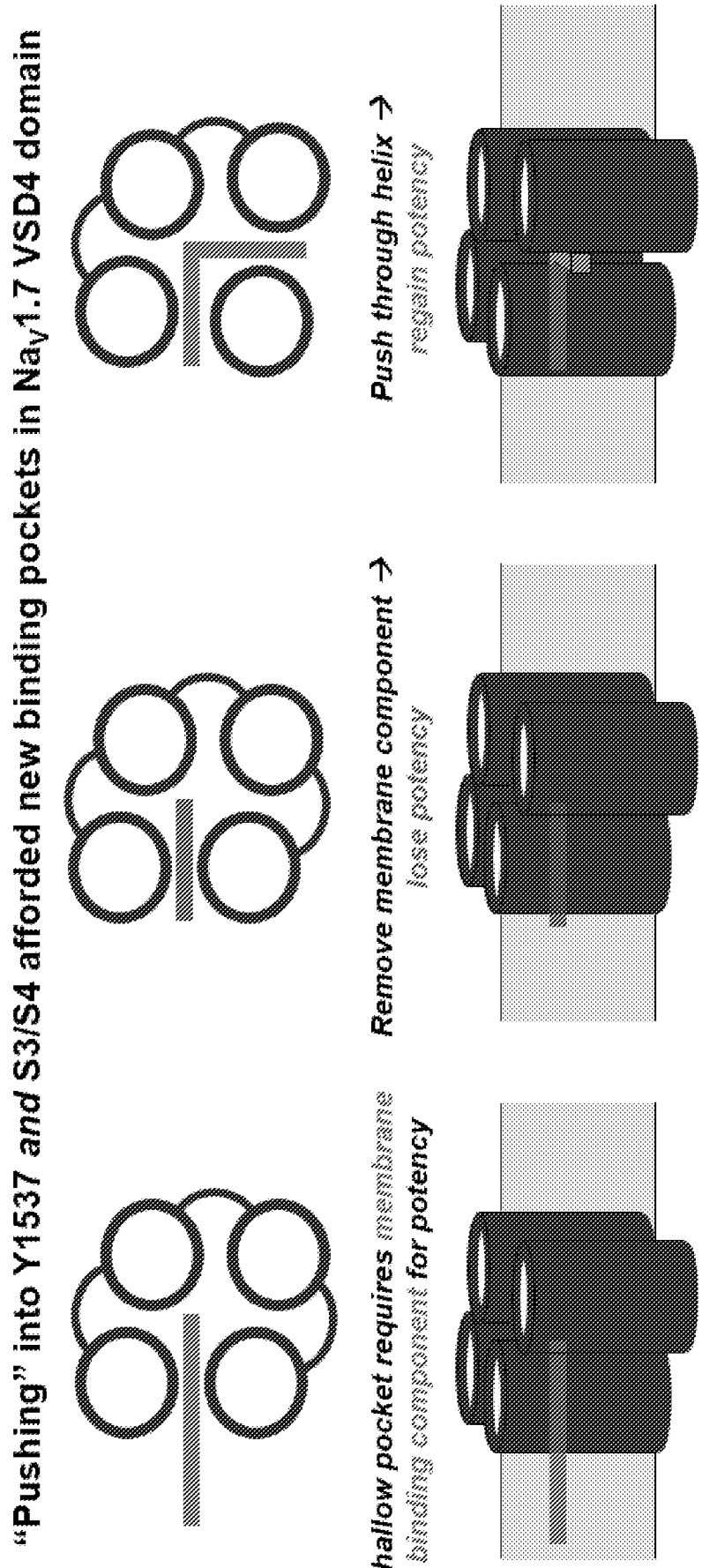

"Pushing" into Y1537 and S3/S4 afforded new binding pockets in $Na_V1.7$ VSD4 domain
Shallow pocket requires membrane binding component for potency
Remove membrane component → lose potency
Push through helix → regain potency

FIG. 8B

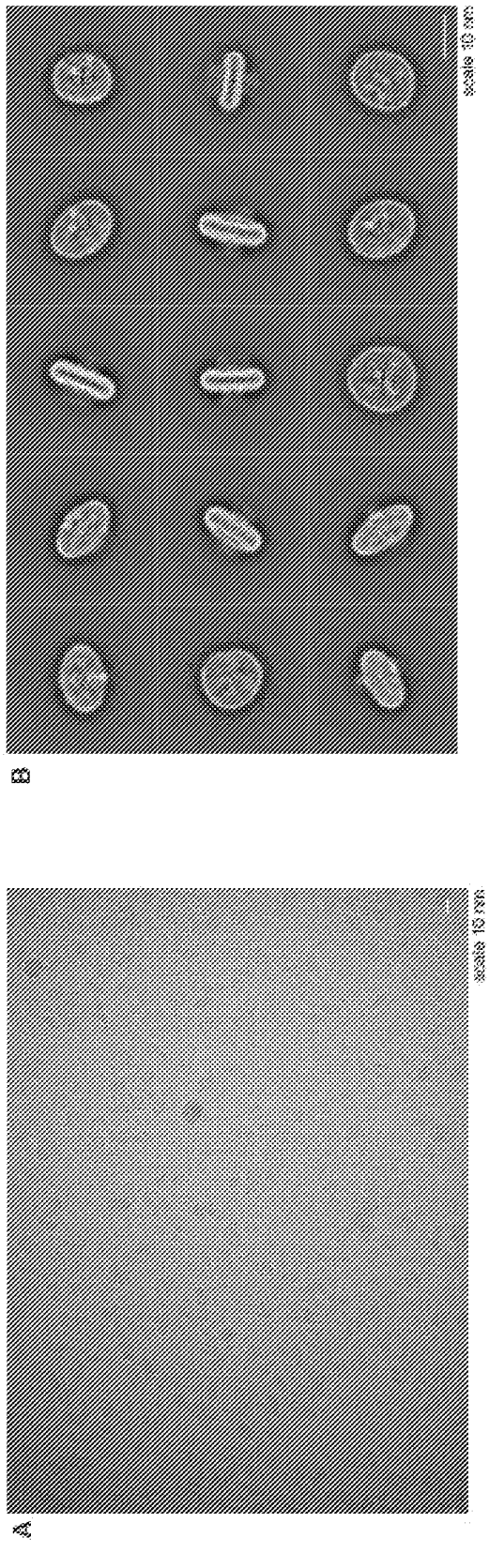


FIG. 9

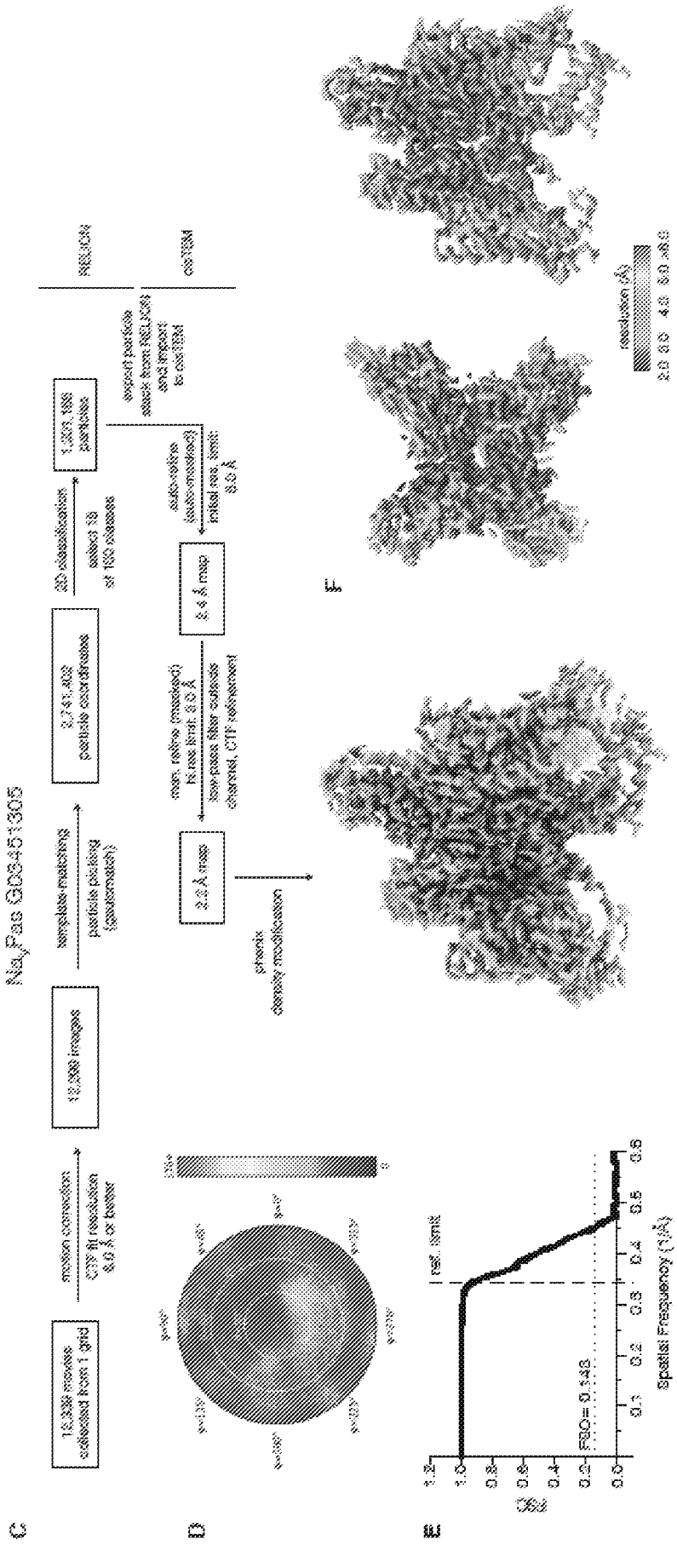

C
D
E
Na$_V$Pas G03451305
motion correction
CTF fit resolution
8.0 Å or better
template matching
particle picking
(gautomatch)
2D classification
select 18
of 150 classes
auto-refine
(gold-standard)
initial res. limit
8.0 Å
post-process
mask, refine (masked)
fit res. limit 8.0 Å
low-pass filter softmask
channel, CTF refinement
phenix
density modification
FSC
ref. limit
FSC= 0.143
Spatial Frequency (1/Å)
resolution (Å)

FIG. 10

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/041258

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D207/08 C07D213/82 C07D307/12 C07C311/51 A61K31/44
A61K31/445 A61K31/18 A61P25/04
ADD.
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)
C07D C07C A61P A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/177224 A1 (GENENTECH INC [US]; XENON PHARMACEUTICALS INC [CA] ET AL.) 28 November 2013 (2013-11-28) paragraph [0004]; claims 1-63; examples 22,352,376,375,388,389,417-419,422-424	1-14, 36-44,47
X	DE 197 42 951 A1 (HOECHST SCHERING AGREVO GMBH [DE]) 15 April 1999 (1999-04-15) Table on page 13 ff., compounds I-1 - I-229; Table on page 21 ff., compounds 2-1 - 2-87; Table on page 25, compounds 3-1 - 3-62;; claims 1-11	1-3,11
X	WO 2012/007869 A2 (PFIZER LTD [GB]; BROWN ALAN DANIEL [GB] ET AL.) 19 January 2012 (2012-01-19) page 68, prepration 9; claims 1-21	1-3,7, 10,11, 36-44,47

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"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
30 November 2022	03/02/2023

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kleidernigg, Oliver

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/041258

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed.

   b. [ ] furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      [ ] accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/041258

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

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

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

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

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

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

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

see additional sheet

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 an 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.:

1-14(completely); 36-44, 47(partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-14(completely); 36-44, 47(partially)

   Compounds of formula (I)

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2. claims: 15(completely); 36-44, 47(partially)

   Compound of example 107

   ---

3. claims: 16-26(completely); 36-44, 47(partially)

   Compound of formula (II)

   ---

4. claims: 27-35(completely); 36-44, 47(partially)

   Compound of formula (III)

   ---

5. claims: 45, 46(completely); 47(partially)

   Computer based method of designing an inhibitor of NaV1.7 and method of identifying a compound that binds to the VSD4 domain of the NaV1.7 receptor

   ---

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2022/041258

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