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(54) **SULFONAMIDES AS MODULATORS OF SODIUM CHANNELS**

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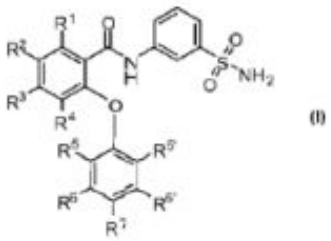
(71) Applicant(s):
VERTEX PHARMACEUTICALS INCORPORATED

(74) Contact:
AJ PARK

(72) Inventor(s):
HADIDA-RUAH, Sara, Sabina
ANDERSON, Corey
ARUMUGAM, Vijayalaksmi
JOHNSON, James, Philip
BEAR, Brian, Richard
TERMIN, Andreas, P.
KRENITSKY, Paul

(57) Abstract:



(I)

The invention relates to compounds of formula I or pharmaceutically acceptable salts thereof, useful as inhibitors of sodium channels: (I). The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various disorders, including pain.

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SULFONAMIDES AS MODULATORS OF SODIUM CHANNELS

TECHNICAL FIELD OF THE INVENTION

[001] The invention relates to compounds useful as inhibitors of sodium channels. The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various disorders including pain.

BACKGROUND OF THE INVENTION

[002] Pain is a protective mechanism that allows healthy animals to avoid tissue damage and to prevent further damage to injured tissue. Nonetheless there are many conditions where pain persists beyond its usefulness, or where patients would benefit from inhibition of pain. Neuropathic pain is a form of chronic pain caused by an injury to the sensory nerves (Dieleman, J.P., et al., Incidence rates and treatment of neuropathic pain conditions in the general population. *Pain*, 2008. **137**(3): p. 681-8). Neuropathic pain can be divided into two categories, pain caused by generalized metabolic damage to the nerve and pain caused by a discrete nerve injury. The metabolic neuropathies include post herpetic neuropathy, diabetic neuropathy, and drug-induced neuropathy. Discrete nerve injuries indications include post amputation pain, post-surgical nerve injury pain, and nerve entrapment injuries like neuropathic back pain.

[003] Voltage-gated sodium channels (Na_V's) play a critical role in pain signaling. Na_V's are key biological mediators of electrical signaling as they are the primary mediators of the rapid upstroke of the action potential of many excitable cell types (e.g. neurons, skeletal myocytes, cardiac myocytes). The evidence for the role of these channels in normal physiology, the pathological states arising from mutations in sodium channel genes, preclinical work in animal models, and the clinical pharmacology of known sodium channel modulating agents all point to the central role of Na_V's in pain sensation (Rush, A.M. and T.R. Cummins, *Painful Research: Identification of a Small-Molecule Inhibitor that Selectively Targets $Na_V1.8$ Sodium Channels.* Mol Interv, 2007. **7**(4): p. 192-5); England, S., Voltage-gated sodium channels: the search for subtype-selective analgesics. *Expert Opin Investig Drugs* **17** (12), p. 1849-64 (2008); Krafte, D. S. and Bannon, A. W., Sodium channels and nociception: recent concepts and therapeutic opportunities. *Curr Opin Pharmacol* **8** (1), p. 50-56 (2008)). Na_V's are the primary mediators of the rapid upstroke of the action potential of many excitable cell types (e.g. neurons,

skeletal myocytes, cardiac myocytes), and thus are critical for the initiation of signaling in those cells (Hille, Bertil, *Ion Channels of Excitable Membranes*, Third ed. (Sinauer Associates, Inc., Sunderland, MA, 2001)). Because of the role Na_V's play in the initiation and propagation of neuronal signals, antagonists that reduce Na_V currents can prevent or reduce neural signaling and Na_V channels have long been considered likely targets to reduce pain in conditions where hyper-excitability is observed (Chahine, M., Chatelier, A., Babich, O., and Krupp, J. J., Voltage-gated sodium channels in neurological disorders. *CNS Neurol Disord Drug Targets* **7** (2), p. 144-58 (2008)). Several clinically useful analgesics have been identified as inhibitors of Na_V channels. The local anesthetic drugs such as lidocaine block pain by inhibiting Na_V channels, and other compounds, such as carbamazepine, lamotrigine, and tricyclic antidepressants that have proven effective at reducing pain have also been suggested to act by sodium channel inhibition (Soderpalm, B., Anticonvulsants: aspects of their mechanisms of action. *Eur J Pain* **6 Suppl A**, p. 3-9 (2002); Wang, G. K., Mitchell, J., and Wang, S. Y., Block of persistent late Na^+ currents by antidepressant sertraline and paroxetine. *J Membr Biol* **222** (2), p. 79-90 (2008)).

[004] The Na_V's form a subfamily of the voltage-gated ion channel super-family and comprises 9 isoforms, designated Nav1.1 –Nav1.9. The tissue localizations of the nine isoforms vary greatly. Nav1.4 is the primary sodium channel of skeletal muscle, and Nav1.5 is primary sodium channel of cardiac myocytes. Na_V's 1.7, 1.8 and 1.9 are primarily localized to the peripheral nervous system, while Na_V's 1.1, 1.2, 1.3, and 1.6 are neuronal channels found in both the central and peripheral nervous systems. The functional behaviors of the nine isoforms are similar but distinct in the specifics of their voltage-dependent and kinetic behavior (Catterall, W. A., Goldin, A. L., and Waxman, S. G., International Union of Pharmacology. XLVII. Nomenclature and structure-function relationships of voltage-gated sodium channels. *Pharmacol Rev* **57** (4), p. 397 (2005)).

[005] Immediately upon their discovery, $Na_V1.8$ channels were identified as likely targets for analgesia (Akopian, A.N., L. Sivilotti, and J.N. Wood, A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons. *Nature*, 1996. **379**(6562): p. 257-62). Since then, $Na_V1.8$ has been shown to be the most significant carrier of the sodium current that maintains action potential firing in small DRG neurons (Blair, N.T. and B.P. Bean, Roles of tetrodotoxin (TTX)-sensitive Na+ current, TTX-resistant Na^+ current, and Ca^{2+} current in the action potentials of nociceptive sensory neurons. *J Neurosci.*, 2002. **22**(23): p. 10277-90). $Na_V1.8$ is essential for spontaneous firing in damaged neurons, like those that drive neuropathic pain (Roza, C., et al., The tetrodotoxin-resistant Na^+ channel $Na_V1.8$ is essential for the expression of spontaneous activity in damaged sensory axons of mice. *J. Physiol.*, 2003. **550**(Pt

3): p. 921-6; Jarvis, M.F., et al., A-803467, a potent and selective $Na_V1.8$ sodium channel blocker, attenuates neuropathic and inflammatory pain in the rat. *Proc Natl Acad Sci.* U S A, 2007. **104**(20): p. 8520-5; Joshi, S.K., et al., Involvement of the TTX-resistant sodium channel Nav1.8 in inflammatory and neuropathic,but not post-operative, pain states. *Pain*, 2006. **123**(1-2): pp. 75-82; Lai, J., et al., Inhibition of neuropathic pain by decreased expression of the tetrodotoxin-resistant sodium channel, $Na_V1.8$. *Pain*, 2002. **95**(1-2): p. 143-52; Dong, X.W., et al., Small interfering RNA-mediated selective knockdown of $Na(_V)1.8$ tetrodotoxin-resistant sodium channel reverses mechanical allodynia in neuropathic rats. *Neuroscience*, 2007. **146**(2): p. 812-21; Huang, H.L., et al., Proteomic profiling of neuromas reveals alterations in protein composition and local protein synthesis in hyper-excitable nerves. *Mol Pain*, 2008. **4**: p. 33; Black, J.A., et al., Multiple sodium channel isoforms and mitogen-activated protein kinases are present in painful human neuromas. *Ann Neurol*, 2008. **64**(6): p. 644-53; Coward, K., et al., Immunolocalization of SNS/PN3 and NaN/SNS2 sodium channels in human pain states. *Pain*, 2000. **85**(1-2): p. 41-50; Yiangou, Y., et al., SNS/PN3 and SNS2/NaN sodium channel-like immunoreactivity in human adult and neonate injured sensory nerves. *FEBS Lett*, 2000. **467**(2-3): p. 249-52; Ruangsri, S., et al., Relationship of axonal voltage-gated sodium channel 1.8 ($Na_V1.8$) mRNA accumulation to sciatic nerve injury-induced painful neuropathy in rats. *J Biol Chem*. **286**(46): p. 39836-47). The small DRG neurons where $Na_V1.8$ is expressed include the nociceptors critical for pain signaling. $Na_V1.8$ is the primary channel that mediates large amplitude action potentials in small neurons of the dorsal root ganglia (Blair, N.T. and B.P. Bean, Roles of tetrodotoxin (TTX)-sensitive Na^+ current, TTX-resistant Na^+ current, and Ca^{2+} current in the action potentials of nociceptive sensory neurons. *J Neurosci*., 2002. **22**(23): p. 10277-90). $Na_V1.8$ is necessary for rapid repetitive action potentials in nociceptors, and for spontaneous activity of damaged neurons. (Choi, J.S. and S.G. Waxman, Physiological interactions between $Na_V1.7$ and $Na_V1.8$ sodium channels: a computer simulation study. *J Neurophysiol*. **106**(6): p. 3173-84; Renganathan, M., T.R. Cummins, and S.G. Waxman, Contribution of $Na(_V)1.8$ sodium channels to action potential electrogenesis in DRG neurons. *J Neurophysiol*., 2001. **86**(2): p. 629-40; Roza, C., et al., The tetrodotoxin-resistant Na^+ channel $Na_V1.8$ is essential for the expression of spontaneous activity in damaged sensory axons of mice. *J Physiol*., 2003. **550**(Pt 3): p. 921-6). In depolarized or damaged DRG neurons, $Na_V1.8$ appears to be the primary driver of hyper-excitablility (Rush, A.M., et al., A single sodium channel mutation produces hyper- or hypoexcitability in different types of neurons. *Proc Natl Acad Sci USA*, 2006. **103**(21): p. 8245-50). In some animal pain models, $Na_V1.8$ mRNA expression levels have been shown to increase in the DRG (Sun, W., et al., Reduced conduction failure of the main

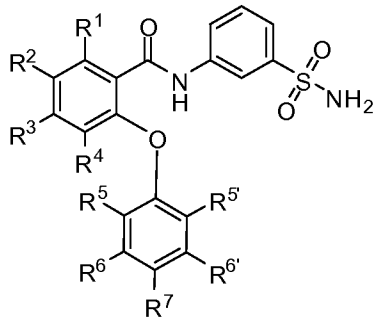
axon of polymodal nociceptive C-fibres contributes to painful diabetic neuropathy in rats. *Brain.* **135**(Pt 2): p. 359-75; Strickland, I.T., et al., Changes in the expression of NaV1.7, $Na_V1.8$ and $Na_V1.9$ in a distinct population of dorsal root ganglia innervating the rat knee joint in a model of chronic inflammatory joint pain. *Eur J Pain*, 2008. **12**(5): p. 564-72; Qiu, F., et al., Increased expression of tetrodotoxin-resistant sodium channels $Na_V1.8$ and $Na_V1.9$ within dorsal root ganglia in a rat model of bone cancer pain. *Neurosci. Lett.* **512**(2): p. 61-6).

[006] The primary drawback to the known Na_V inhibitors is their poor therapeutic window, and this is likely a consequence of their lack of isoform selectivity. Since $Na_V1.8$ is primarily restricted to the neurons that sense pain, selective $Na_V1.8$ blockers are unlikely to induce the adverse events common to non-selective Na_V blockers. Accordingly, there remains a need to develop additional Na_V channel antagonists preferably those that are more Nav1.8 selective and more potent with increased metabolic stability and with fewer side effects.

SUMMARY OF THE INVENTION

[007] It has now been found that compounds of this invention, and pharmaceutically acceptable salts and compositions thereof, are useful as inhibitors of voltage-gated sodium channels.

[008] These compounds have the general formula **I**:



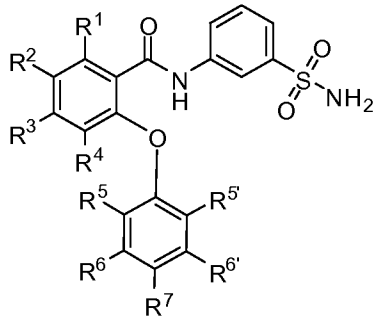
I;

or a pharmaceutically acceptable salt thereof.

[009] These compounds and pharmaceutically acceptable salts and compositions are useful for treating or lessening the severity of a variety of diseases, disorders, or conditions, including, but not limited to, chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence or cardiac arrhythmia.

Detailed Description of the Invention

[0010] In one aspect, the invention provides compounds of formula **I**:



I;

or a pharmaceutically acceptable salt thereof,

wherein, independently for each occurrence:

R^1 is H, Cl, CH_3, CF_3 or cyclopropyl;

R^2 is H, F, Cl, CN, CH_3, CF_3 or CHF_2;

R^3 is H, F, Cl, CN, CF_3, OCF_3 or CF_2CF_3;

R^4 is H;

R^5 is H, F, Cl, CH_3, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$ or $OCHF_2$;

$R^{5'}$ is H, F, Cl, CH_3, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$ or $OCHF_2$;

R^6 is H, F or Cl;

$R^{6'}$ is H, F or Cl; and

R^7 is H, F, Cl, OCH_3, OCF_3, OCH_2CH_3, $OCH(CH_3)_2$ or $OCHF_2$,

provided that R^1, R^2, and R^3 are not simultaneously hydrogen; and

that R^5, $R^{5'}$, R^6, $R^{6'}$, and R^7 are not simultaneously hydrogen.

[0011] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry," Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry," 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0012] As described herein, compounds of the invention can optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by

particular classes, subclasses, and species of the invention. As described herein, the variables in formula I encompass specific groups, such as, for example, alkyl and cycloalkyl. As one of ordinary skill in the art will recognize, combinations of substituents envisioned by this invention are those combinations that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[0013] The phrase "optionally substituted" may be used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted," whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Specific substituents are described above in the definitions and below in the description of compounds and examples thereof. Unless otherwise indicated, an optionally substituted group can have a substituent at each substitutable position of the group, and when more than one position in any given structure can be substituted with more than one substituent selected from a specified group, the substituent can be either the same or different at every position. A ring substituent, such as a heterocycloalkyl, can be bound to another ring, such as a cycloalkyl, to form a spiro-bicyclic ring system, e.g., both rings share one common atom. As one of ordinary skill in the art will recognize, combinations of substituents envisioned by this invention are those combinations that result in the formation of stable or chemically feasible compounds.

[0014] The phrase "up to," as used herein, refers to zero or any integer number that is equal or less than the number following the phrase. For example, "up to 4" means any one of 0, 1, 2, 3, and 4.

[0015] The term "aliphatic," "aliphatic group" or "alkyl" as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation. Unless otherwise specified, aliphatic groups contain 1 – 20 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1 – 10 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1 – 8 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1 – 6 aliphatic carbon atoms, and in yet other embodi ments aliphatic groups contain 1 – 4 aliphatic

carbon atoms. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups.

[0016] The terms "cycloaliphatic" or "cycloalkyl" mean a monocyclic hydrocarbon ring, or a polycyclic hydrocarbon ring system that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic and has a single point of attachment to the rest of the molecule.

[0017] The term "polycyclic ring system," as used herein, includes bicyclic and tricyclic 4- to 12- membered structures that form at least two rings, wherein the two rings have at least one atom in common (e.g., 2 atoms in common) including fused, bridged, or spirocyclic ring systems.

[0018] The term "halogen" or "halo" as used herein, means F, Cl, Br or I.

[0019] Unless otherwise specified, the term "heterocycle," "heterocyclyl," "heterocycloaliphatic," "heterocycloalkyl," or "heterocyclic" as used herein means non-aromatic, monocyclic, bicyclic, or tricyclic ring systems in which one or more ring atoms in one or more ring members is an independently selected heteroatom. Heterocyclic ring can be saturated or can contain one or more unsaturated bonds. In some embodiments, the "heterocycle," "heterocyclyl," "heterocycloaliphatic," "heterocycloalkyl," or "heterocyclic" group has three to fourteen ring members in which one or more ring members is a heteroatom independently selected from oxygen, sulfur, nitrogen, or phosphorus, and each ring in the ring system contains 3 to 7 ring members.

[0020] The term "heteroatom" means oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0021] The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation but is not aromatic.

[0022] The term "alkoxy," or "thioalkyl," as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen ("alkoxy") or sulfur ("thioalkyl") atom.

[0023] The term "aryl" used alone or as part of a larger moiety as in "aralkyl," "aralkoxy," or "aryloxyalkyl," refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring carbon atoms, wherein at least one ring in the system is aromatic

and wherein each ring in the system contains 3 to 7 ring carbon atoms. The term "aryl" may be used interchangeably with the term "aryl ring."

[0024] The term "heteroaryl," used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy," refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 3 to 7 ring members. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic."

[0025] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Thus, included within the scope of the invention are tautomers of compounds of formula I. The structures also include zwitterionic forms of the compounds or salts of formula I where appropriate.

[0026] Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched or isotopically-labeled atoms. The isotopically-labeled compounds may have one or more atoms replaced by an atom having an atomic mass or mass number usually found in nature. Examples of isotopes present in compounds of formula I include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as, but not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S and ^{18}F. Certain isotopically-labeled compounds of formula I, in addition to being useful as as therapuetic agents, are also useful in drug and/or substrate tissue distribution assays, as analytical tools or as probes in other biological assays. In one aspect of the present invention, tritiated (e.g., ^{3}H) and carbon-14 (e.g., ^{14}C) isotopes are useful given their ease of detectability. In another aspect of the present invention, replacement of one or more hydrogen atoms with heavier isotopes such as deuterium, (e.g., ^{2}H) can afford certain therapeutic advantages.

[0027] In one embodiment, the invention features a compound of formula I and the attendant definitions, wherein R^1 is H. In another embodiment, R^1 is Cl. In another embodiment, R^1 is CH_3. In another embodiment, R^1 is CF_3. In another embodiment, R^1 is

cyclopropyl. In another embodiment, R^1 is H, CF_3 or Cl. In another embodiment, R^1 is H or CF_3.

[0028] In another embodiment, the invention features a compound of formula I and the attendant definitions, wherein R^2 is H. In another embodiment, R^2 is F. In another embodiment, R^2 is Cl. In another embodiment, R^2 is CN. In another embodiment, R^2 is CH_3. In another embodiment, R^2 is CF_3. In another embodiment, R^2 is CHF_2. In another embodiment, R^2 is H, CF_3 or Cl. In another embodiment, R^2 is H or CF_3.

[0029] In another embodiment, the invention features a compound of formula I and the attendant definitions, wherein R^3 is H. In another embodiment, R^3 is F. In another embodiment, R^3 is Cl. In another embodiment, R^3 is CN. In another embodiment, R^3 is CF_3. In another embodiment, R^3 is OCF_3. In another embodiment, R^3 is CF_2CF_3. In another embodiment, R^3 is H, CF_3, Cl or OCF_3. In another embodiment, R^3 is H, CF_3 or Cl.

[0030] In another embodiment, the invention features a compound of formula I and the attendant definitions, wherein R^5 is H. In another embodiment, R^5 is F. In another embodiment, R^5 is Cl. In another embodiment, R^5 is CH_3. In another embodiment, R^5 is OCH_3. In another embodiment, R^5 is OCH_2CH_3. In another embodiment, R^5 is $OCH_2CH_2CH_3$. In another embodiment, R^5 is $OCHF_2$.

[0031] In another embodiment, the invention features a compound of formula I and the attendant definitions, wherein $R^{5'}$ is H. In another embodiment, $R^{5'}$ is F. In another embodiment, $R^{5'}$ is Cl. In another embodiment, $R^{5'}$ is CH_3. In another embodiment, $R^{5'}$ is OCH_3. In another embodiment, $R^{5'}$ is OCH_2CH_3. In another embodiment, $R^{5'}$ is $OCH_2CH_2CH_3$. In another embodiment, $R^{5'}$ is $OCHF_2$.

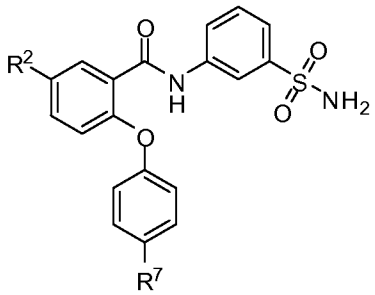
[0032] In another embodiment, the invention features a compound of formula I and the attendant definitions, wherein R^6 is H. In another embodiment, R^6 is F. In another embodiment, R^6 is Cl. In another embodiment, R^6 is H or F.

[0033] In another embodiment, the invention features a compound of formula I and the attendant definitions, wherein $R^{6'}$ is H. In another embodiment, $R^{6'}$ is F. In another embodiment, $R^{6'}$ is Cl. In another embodiment, $R^{6'}$ is H or F.

[0034] In another embodiment, the invention features a compound of formula I and the attendant definitions, wherein R^7 is H. In another embodiment, R^7 is F. In another embodiment, R^7 is Cl. In another embodiment, R^7 is OCH_3. In another embodiment, R^7 is OCF_3. In another embodiment, R^7 is OCH_2CH_3. In another embodiment, R^7 is $OCH(CH_3)_2$. In another

embodiment, R^7 is $OCHF_2$. In another embodiment, R^7 is F, Cl, OCH_3 or OCF_3. In another embodiment, R^7 is F or OCH_3.

[0035] In another aspect, the invention provides a compound of formula **I-A**:



I-A

or a pharmaceutically acceptable salt thereof,

wherein, independently for each occurrence:

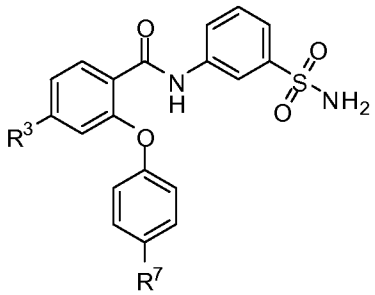
R^2 is F, Cl, CN, CH_3, CF_3 or CHF_2; and

R^7 is F, Cl, OCH_3, OCF_3, OCH_2CH_3, $OCH(CH_3)_2$ or $OCHF_2$.

[0036] In one embodiment, the invention features a compound of formula I-A and the attendant definitions, wherein R^2 is F. In another embodiment, R^2 is Cl. In another embodiment, R^2 is CN. In another embodiment, R^2 is CH_3. In another embodiment, R^2 is CF_3. In another embodiment, R^2 is CHF_2.

[0037] In another embodiment, the invention features a compound of formula I-A and the attendant definitions, wherein R^7 is F. In another embodiment, R^7 is Cl. In another embodiment, R^7 is OCH_3. In another embodiment, R^7 is OCF_3, In another embodiment, R^7 is OCH_2CH_3. In another embodiment, R^7 is $OCH(CH_3)_2$. In another embodiment, R^7 is $OCHF_2$.

[0038] In another aspect, the invention provides a compound of formula **I-B**:



I-B

or a pharmaceutically acceptable salt thereof,

wherein, independently for each occurrence:

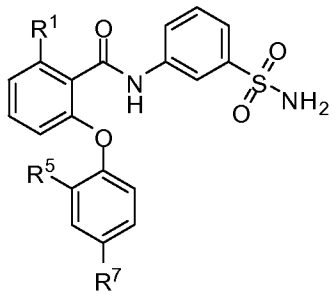
R^3 is F, Cl, CN, CF_3, OCF_3 or CF_2CF_3; and

R^7 is F, Cl, OCH_3, OCF_3, OCH_2CH_3, $OCH(CH_3)_2$ or $OCHF_2$.

[0039] In one embodiment, the invention features a compound of formula I-B and the attendant definitions, wherein R^3 is F. In another embodiment, R^3 is Cl. In another embodiment, R^3 is CN. In another embodiment, R^3 is CF_3. In another embodiment, R^3 is OCF_3. In another embodiment, R^3 is CF_2CF_3.

[0040] In another embodiment, the invention features a compound of formula I-B and the attendant definitions, wherein R^7 is F. In another embodiment, R^7 is Cl. In another embodiment, R^7 is OCH_3. In another embodiment, R^7 is OCF_3. In another embodiment, R^7 is OCH_2CH_3. In another embodiment, R^7 is $OCH(CH_3)_2$. In another embodiment, R^7 is $OCHF_2$.

[0041] In another aspect, the invention provides a compound of formula **I-C**:



I-C

or a pharmaceutically acceptable salt thereof,

wherein, independently for each occurrence:

R^1 is Cl, CH_3, CF_3 or cyclopropyl;

R^5 is F, Cl, CH_3, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$ or $OCHF_2$; and

R^7 is F, Cl, OCH_3, OCH_2CH_3, $OCH(CH_3)_2$ or $OCHF_2$.

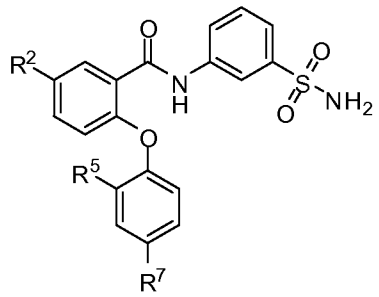
[0042] In one embodiment, the invention features a compound of formula I-C and the attendant definitions, wherein R^1 is Cl. In another embodiment, R^1 is CH_3. In another embodiment, R^1 is CF_3. In another embodiment, R^1 is cyclopropyl.

[0043] In another embodiment, the invention features a compound of formula I-C and the attendant definitions, wherein R^5 is F. In another embodiment, R^5 is Cl. In another embodiment, R^5 is CH_3. In another embodiment, R^5 is OCH_3. In another embodiment, R^5 is OCH_2CH_3. In

another embodiment, R^5 is $OCH_2CH_2CH_3$. In another embodiment, R^5 is $OCHF_2$.

[0044] In another embodiment, the invention features a compound of formula I-C and the attendant definitions, wherein R^7 is F. In another embodiment, R^7 is Cl. In another embodiment, R^7 is OCH_3. In another embodiment, R^7 is OCH_2CH_3. In another embodiment, R^7 is $OCH(CH_3)_2$. In another embodiment, R^7 is $OCHF_2$.

[0045] In another aspect, the invention provides a compound of formula **I-D**:



I-D

or a pharmaceutically acceptable salt thereof,

wherein, independently for each occurrence:

R^2 is F, Cl, CN, CH_3, CF_3 or CHF_2;

R^5 is F, Cl, CH_3, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$ or $OCHF_2$; and

R^7 is F, Cl, OCH_3, OCF_3, OCH_2CH_3, $OCH(CH_3)_2$ or $OCHF_2$.

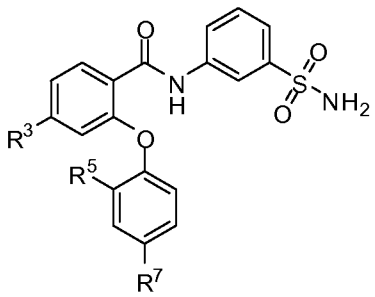
[0046] In one embodiment, the invention features a compound of formula I-D and the attendant definitions, wherein R^2 is F. In another embodiment, R^2 is Cl. In another embodiment, R^2 is CN. In another embodiment, R^2 is CH_3. In another embodiment, R^2 is CF_3. In another embodiment, R^2 is CHF_2. In another embodiment, R^2 is Cl or CF_3.

[0047] In another embodiment, the invention features a compound of formula I-D and the attendant definitions, wherein R^5 is F. In another embodiment, R^5 is Cl. In another embodiment, R^5 is CH_3. In another embodiment, R^5 is OCH_3. In another embodiment, R^5 is OCH_2CH_3. In another embodiment, R^5 is $OCH_2CH_2CH_3$. In another embodiment, R^5 is $OCHF_2$. In another embodiment, R^5 is F, Cl, CH_3 or OCH_3.

[0048] In another embodiment, the invention features a compound of formula I-D and the attendant definitions, wherein R^7 is F. In another embodiment, R^7 is Cl. In another embodiment, R^7 is OCH_3. In another embodiment, R^7 is OCF_3. In another embodiment, R^7 is OCH_2CH_3. In another embodiment, R^7 is $OCH(CH_3)_2$. In another embodiment, R^7 is $OCHF_2$. In another

embodiment, R^7 is F, Cl, OCH_3 or OCF_3.

[0049] In another aspect, the invention provides a compound of formula **I-E**:



I-E

or a pharmaceutically acceptable salt thereof,

wherein, independently for each occurrence:

R^3 is F, Cl, CN, CF_3, OCF_3 or CF_2CF_3;

R^5 is F, Cl, CH_3, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$ or $OCHF_2$; and

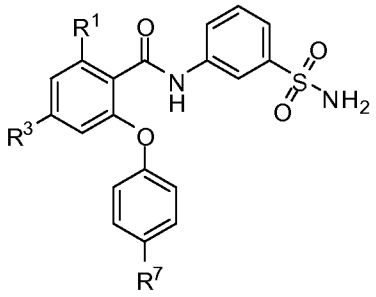
R^7 is F, Cl, OCH_3, OCF_3, OCH_2CH_3, $OCH(CH_3)_2$ or $OCHF_2$.

[0050] In one embodiment, the invention features a compound of formula I-E and the attendant definitions, wherein R^3 is F. In another embodiment, R^3 is Cl. In another embodiment, R^3 is CN. In another embodiment, R^3 is CF_3. In another embodiment, R^3 is OCF_3. In another embodiment, R^3 is CF_2CF_3. In another embodiment, R^3 is Cl, CF_3 or OCF_3.

[0051] In another embodiment, the invention features a compound of formula I-E and the attendant definitions, wherein R^5 is F. In another embodiment, R^5 is Cl. In another embodiment, R^5 is CH_3. In another embodiment, R^5 is OCH_3. In another embodiment, R^5 is OCH_2CH_3. In another embodiment, R^5 is $OCH_2CH_2CH_3$. In another embodiment, R^5 is $OCHF_2$. In another embodiment, R^5 is F, Cl, CH_3 or OCH_3.

[0052] In another embodiment, the invention features a compound of formula I-E and the attendant definitions, wherein R^7 is F. In another embodiment, R^7 is Cl. In another embodiment, R^7 is OCH_3. In another embodiment, R^7 is OCF_3. In another embodiment, R^7 is OCH_2CH_3. In another embodiment, R^7 is $OCH(CH_3)_2$. In another embodiment, R^7 is $OCHF_2$. In another embodiment, R^7 is F, Cl, OCH_3 or OCF_3.

[0053] In another aspect, the invention provides a compound of formula **I-F**:



I-F

or a pharmaceutically acceptable salt thereof,

wherein, independently for each occurrence:

R^1 is Cl, CH_3, CF_3 or cyclopropyl;

R^3 is F, Cl, CN, CF_3, OCF_3 or CF_2CF_3; and

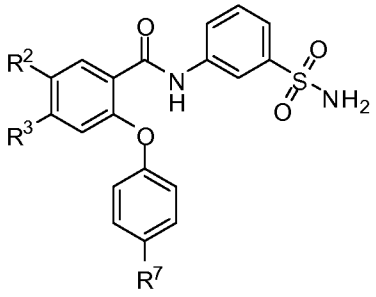
R^7 is F, Cl, OCH_3, OCF_3, OCH_2CH_3, $OCH(CH_3)_2$ or $OCHF_2$.

[0054] In one embodiment, the invention features a compound of formula I-F and the attendant definitions, wherein R^1 is Cl. In another embodiment, R^1 is CH_3. In another embodiment, R^1 is CF_3. In another embodiment, R^1 is cyclopropyl.

[0055] In another embodiment, the invention features a compound of formula I-F and the attendant definitions, wherein R^3 is F. In another embodiment, R^3 is Cl. In another embodiment, R^3 is CN. In another embodiment, R^3 is CF_3. In another embodiment, R^3 is OCF_3. In another embodiment, R^3 is CF_2CF_3.

[0056] In another embodiment, the invention features a compound of formula I-F and the attendant definitions, wherein R^7 is F. In another embodiment, R^7 is Cl. In another embodiment, R^7 is OCH_3. In another embodiment, R^7 is OCF_3. In another embodiment, R^7 is OCH_2CH_3. In another embodiment, R^7 is $OCH(CH_3)_2$. In another embodiment, R^7 is $OCHF_2$.

[0057] In another aspect, the invention provides a compound of formula **I-G**:



I-G

or a pharmaceutically acceptable salt thereof,

wherein, independently for each occurrence:

R^2 is F, Cl, CN, CH_3, CF_3 or CHF_2;

R^3 is F, Cl, CN, CF_3, OCF_3 or CF_2CF_3; and

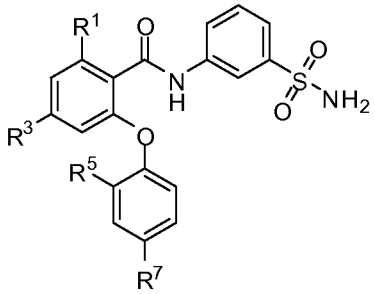
R^7 is F, Cl, OCH_3, OCF_3, OCH_2CH_3, $OCH(CH_3)_2$ or $OCHF_2$.

[0058] In one embodiment, the invention features a compound of formula I-G and the attendant definitions, wherein R^2 is F. In another embodiment, R^2 is Cl. In another embodiment, R^2 is CN. In another embodiment, R^2 is CH_3. In another embodiment, R^2 is CF_3. In another embodiment, R^2 is CHF_2.

[0059] In another embodiment, the invention features a compound of formula I-G and the attendant definitions, wherein R^3 is F. In another embodiment, R^3 is Cl. In another embodiment, R^3 is CN. In another embodiment, R^3 is CF_3. In another embodiment, R^3 is OCF_3. In another embodiment, R^3 is CF_2CF_3.

[0060] In another embodiment, the invention features a compound of formula I-G and the attendant definitions, wherein R^7 is F. In another embodiment, R^7 is Cl. In another embodiment, R^7 is OCH_3. In another embodiment, R^7 is OCF_3. In another embodiment, R^7 is OCH_2CH_3. In another embodiment, R^7 is $OCH(CH_3)_2$. In another embodiment, R^7 is $OCHF_2$.

[0061] In another aspect, the invention provides a compound of formula **I-H**:



I-H

or a pharmaceutically acceptable salt thereof,

wherein, independently for each occurrence:

R^1 is Cl, CH_3, CF_3 or cyclopropyl;

R^3 is F, Cl, CN, CF_3, OCF_3 or CF_2CF_3;

R^5 is F, Cl, CH_3, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$ or $OCHF_2$; and

R^7 is F, Cl, OCH_3, OCF_3, OCH_2CH_3, $OCH(CH_3)_2$ or $OCHF_2$.

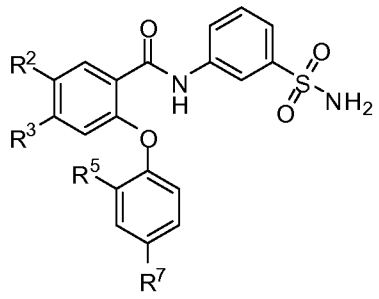
[0062] In one embodiment, the invention features a compound of formula I-H and the attendant definitions, wherein R^1 is Cl. In another embodiment, R^1 is CH_3. In another embodiment, R^1 is CF_3. In another embodiment, R^1 is cyclopropyl.

[0063] In another embodiment, the invention features a compound of formula I-H and the attendant definitions, wherein R^3 is F. In another embodiment, R^3 is Cl. In another embodiment, R^3 is CN. In another embodiment, R^3 is CF_3. In another embodiment, R^3 is OCF_3. In another embodiment, R^3 is CF_2CF_3.

[0064] In another embodiment, the invention features a compound of formula I-H and the attendant definitions, wherein R^5 is F. In another embodiment, R^5 is Cl. In another embodiment, R^5 is CH_3. In another embodiment, R^5 is OCH_3. In another embodiment, R^5 is OCH_2CH_3. In another embodiment, R^5 is $OCH_2CH_2CH_3$. In another embodiment, R^5 is $OCHF_2$.

[0065] In another embodiment, the invention features a compound of formula I-H and the attendant definitions, wherein R^7 is F. In another embodiment, R^7 is F. In another embodiment, R^7 is Cl. In another embodiment, R^7 is OCH_3. In another embodiment, R^7 is OCF_3. In another embodiment, R^7 is OCH_2CH_3. In another embodiment, R^7 is $OCH(CH_3)_2$. In another embodiment, R^7 is $OCHF_2$.

[0066] In another aspect, the invention provides a compound of formula **I-J**:



I-J

or a pharmaceutically acceptable salt thereof,

wherein, independently for each occurrence:

R^2 is F, Cl, CN, CH_3, CF_3 or CHF_2;

R^3 is F, Cl, CN, CF_3, OCF_3 or CF_2CF_3;

R^5 is F, Cl, CH_3, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$ or $OCHF_2$; and

R^7 is F, Cl, OCH_3, OCF_3, OCH_2CH_3, $OCH(CH_3)_2$ or $OCHF_2$.

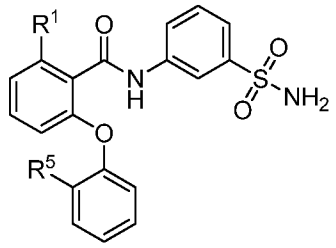
[0067] In one embodiment, the invention features a compound of formula I-J and the attendant definitions, wherein R^2 is F. In another embodiment, R^2 is Cl. In another embodiment, R^2 is CN. In another embodiment, R^2 is CH_3. In another embodiment, R^2 is CF_3. In another embodiment, R^2 is CHF_2.

[0068] In another embodiment, the invention features a compound of formula I-J and the attendant definitions, wherein R^3 is F. In another embodiment, R^3 is Cl. In another embodiment, R^3 is CN. In another embodiment, R^3 is CF_3. In another embodiment, R^3 is OCF_3. In another embodiment, R^3 is CF_2CF_3.

[0069] In another embodiment, the invention features a compound of formula I-J and the attendant definitions, wherein R^5 is F. In another embodiment, R^5 is Cl. In another embodiment, R^5 is CH_3. In another embodiment, R^5 is OCH_3. In another embodiment, R^5 is OCH_2CH_3. In another embodiment, R^5 is $OCH_2CH_2CH_3$. In another embodiment, R^5 is $OCHF_2$.

[0070] In another embodiment, the invention features a compound of formula I-J and the attendant definitions, wherein R^7 is F. In another embodiment, R^7 is Cl. In another embodiment, R^7 is OCH_3. In another embodiment, R^7 is OCF_3. In another embodiment, R^7 is OCH_2CH_3. In another embodiment, R^7 is $OCH(CH_3)_2$. In another embodiment, R^7 is $OCHF_2$.

[0071] In another aspect, the invention provides a compound of formula **I-K**



I-K

or a pharmaceutically acceptable salt thereof,

wherein, independently for each occurrence:

R^1 is Cl, CH_3, CF_3 or cyclopropyl; and

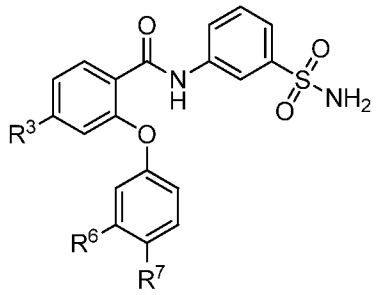
R^5 is F, Cl, CH_3, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$ or $OCHF_2$;

[0072] In another embodiment, the invention features a compound of formula I-K and the attendant definitions, wherein R^1 is Cl. In another embodiment, R^1 is CH_3. In another embodiment, R^1 is CF_3. In another embodiment, R^1 is cyclopropyl.

[0073] In another embodiment, the invention features a compound of formula I-K and the

attendant definitions, wherein R^5 is F. In another embodiment, R^5 is Cl. In another embodiment, R^5 is CH_3. In another embodiment, R^5 is OCH_3. In another embodiment, R^5 is OCH_2CH_3. In another embodiment, R^5 is $OCH_2CH_2CH_3$. In another embodiment, R^5 is $OCHF_2$.

[0074] In another aspect, the invention provides a compound of formula **I-L**



I-L

or a pharmaceutically acceptable salt thereof,

wherein, independently for each occurrence:

R^3 is F, Cl, CN, CF_3, OCF_3 or CF_2CF_3;

R^6 is F or Cl; and

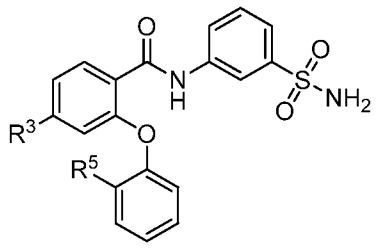
R^7 is F, Cl, OCH_3, OCF_3, OCH_2CH_3, $OCH(CH_3)_2$ or $OCHF_2$.

[0075] In another embodiment, the invention features a compound of formula I-L and the attendant definitions, wherein R^3 is F. In another embodiment, R^3 is Cl. In another embodiment, R^3 is CN. In another embodiment, R^3 is CF_3. In another embodiment, R^3 is OCF_3. In another embodiment, R^3 is CF_2CF_3.

[0076] In another embodiment, the invention features a compound of formula I-L and the attendant definitions, wherein R^6 is F. In another embodiment, R^6 is Cl.

[0077] In another embodiment, the invention features a compound of formula I-L and the attendant definitions, wherein R^7 is F. In another embodiment, R^7 is Cl. In another embodiment, R^7 is OCH_3. In another embodiment, R^7 is OCF_3. In another embodiment, R^7 is OCH_2CH_3. In another embodiment, R^7 is $OCH(CH_3)_2$. In another embodiment, R^7 is $OCHF_2$.

[0078] In another aspect, the invention provides a compound of formula **I-M**



I-M

or a pharmaceutically acceptable salt thereof,

wherein, independently for each occurrence:

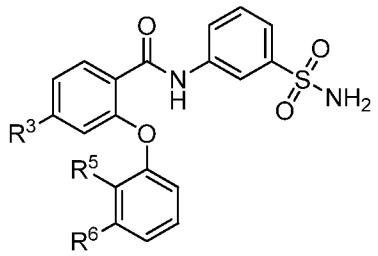
R^3 is F, Cl, CN, CF_3, OCF_3 or CF_2CF_3; and

R^5 is F, Cl, CH_3, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$ or $OCHF_2$.

[0079] In another embodiment, the invention features a compound of formula I-M and the attendant definitions, wherein R^3 is F. In another embodiment, R^3 is Cl. In another embodiment, R^3 is CN. In another embodiment, R^3 is CF_3. In another embodiment, R^3 is OCF_3. In another embodiment, R^3 is CF_2CF_3.

[0080] In another embodiment, the invention features a compound of formula I-M and the attendant definitions, wherein R^5 is F. In another embodiment, R^5 is Cl. In another embodiment, R^5 is CH_3. In another embodiment, R^5 is OCH_3. In another embodiment, R^5 is OCH_2CH_3. In another embodiment, R^5 is $OCH_2CH_2CH_3$. In another embodiment, R^5 is $OCHF_2$.

[0081] In another aspect, the invention provides a compound of formula **I-N**



I-N

or a pharmaceutically acceptable salt thereof,

wherein, independently for each occurrence:

R^3 is F, Cl, CN, CF_3, OCF_3 or CF_2CF_3;

R^5 is F, Cl, CH_3, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$ or $OCHF_2$; and

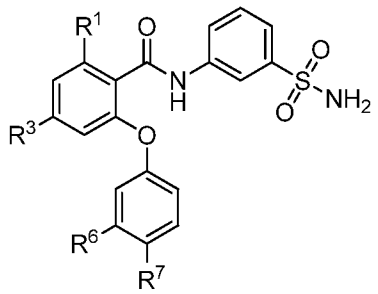
R^6 is F or Cl.

[0082] In another embodiment, the invention features a compound of formula I-N and the attendant definitions, wherein R^3 is F. In another embodiment, R^3 is Cl. In another embodiment, R^3 is CN. In another embodiment, R^3 is CF_3. In another embodiment, R^3 is OCF_3. In another embodiment, R^3 is CF_2CF_3.

[0083] In another embodiment, the invention features a compound of formula I-N and the attendant definitions, wherein R^5 is F. In another embodiment, R^5 is Cl. In another embodiment, R^5 is CH_3. In another embodiment, R^5 is OCH_3. In another embodiment, R^5 is OCH_2CH_3. In another embodiment, R^5 is $OCH_2CH_2CH_3$. In another embodiment, R^5 is $OCHF_2$.

[0084] In another embodiment, the invention features a compound of formula I-N and the attendant definitions, wherein R^6 is F. In another embodiment, R^6 is Cl.

[0085] In another aspect, the invention provides a compound of formula **I-O**



I-O

or a pharmaceutically acceptable salt thereof,

wherein, independently for each occurrence:

R^1 is Cl, CH_3, CF_3 or cyclopropyl;

R^3 is F, Cl, CN, CF_3, OCF_3 or CF_2CF_3;

R^6 is F, or Cl; and

R^7 is F, Cl, OCH_3, OCF_3, OCH_2CH_3, $OCH(CH_3)_2$ or $OCHF_2$.

[0086] In another embodiment, the invention features a compound of formula I-O and the attendant definitions, wherein R^1 is Cl. In another embodiment, R^1 is CH_3. In another embodiment, R^1 is CF_3. In another embodiment, R^1 is cyclopropyl.

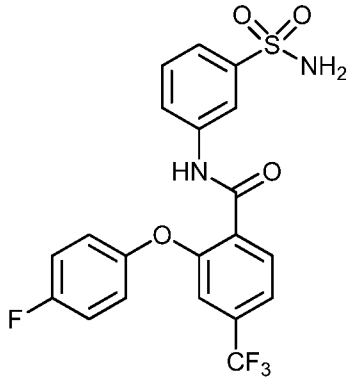
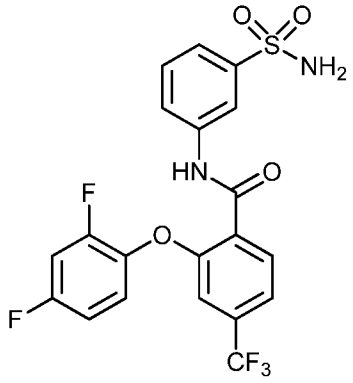
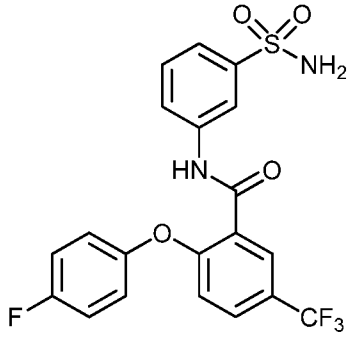
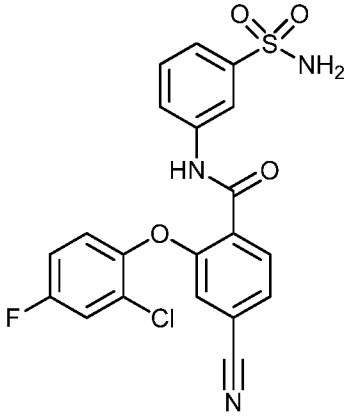
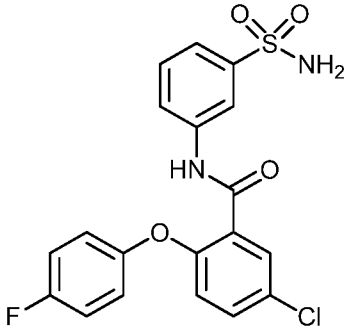
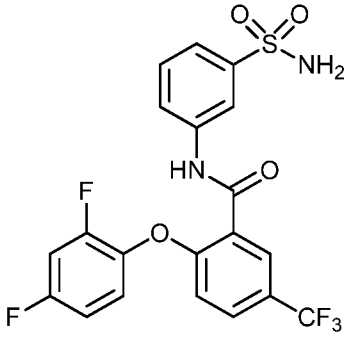
[0087] In another embodiment, the invention features a compound of formula I-O and the attendant definitions, wherein R^3 is F. In another embodiment, R^3 is Cl. In another embodiment, R^3 is CN. In another embodiment, R^3 is CF_3. In another embodiment, R^3 is OCF_3. In another embodiment, R^3 is CF_2CF_3.

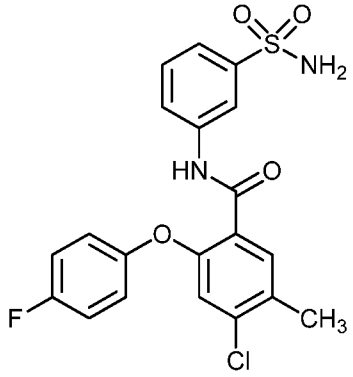
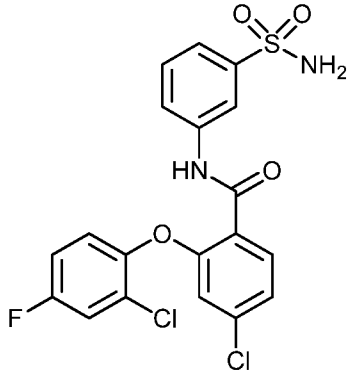
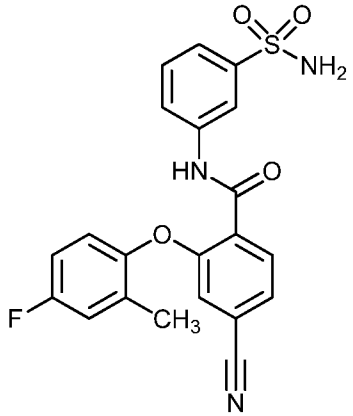
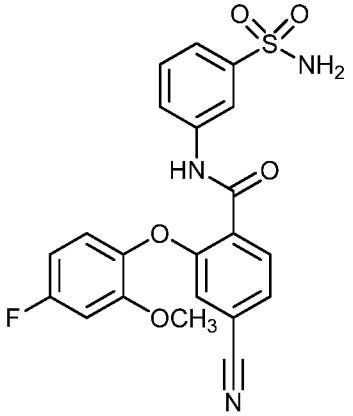
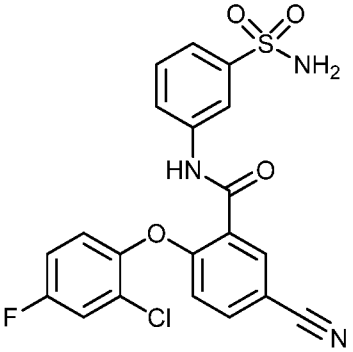
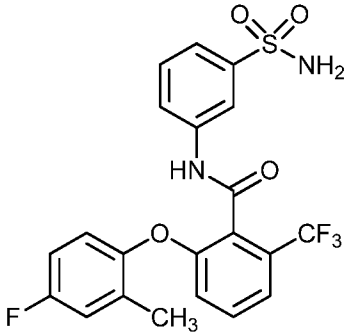
[0088] In another embodiment, the invention features a compound of formula I-O and the attendant definitions, wherein R^6 is F. In another embodiment, R^6 is Cl.

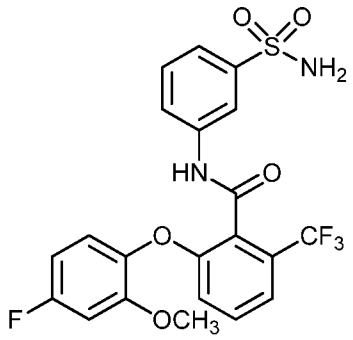
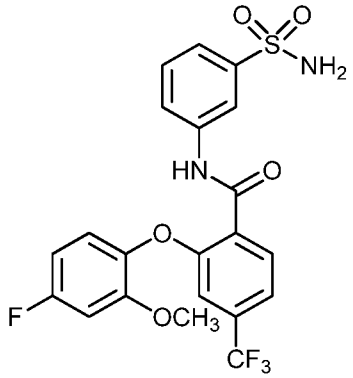
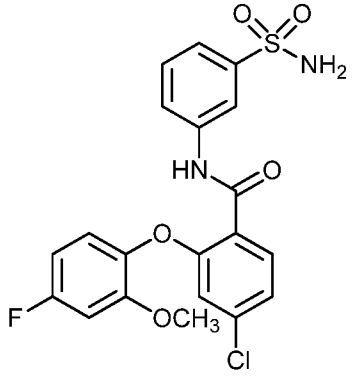
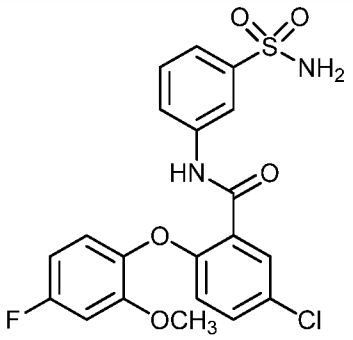
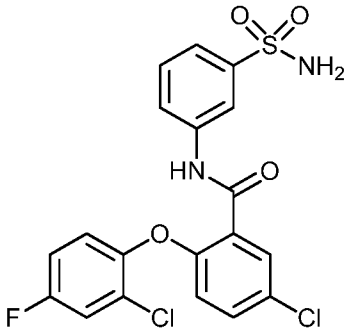
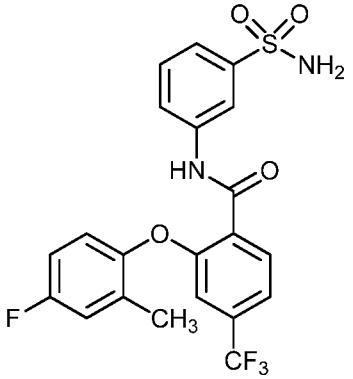
[0089] In another embodiment, the invention features a compound of formula I-O and the attendant definitions, wherein R^7 is F. In another embodiment, R^7 is Cl. In another embodiment, R^7 is OCH_3. In another embodiment, R^7 is OCF_3. In another embodiment, R^7 is OCH_2CH_3. In another embodiment, R^7 is $OCH(CH_3)_2$. In another embodiment, R^7 is $OCHF_2$.

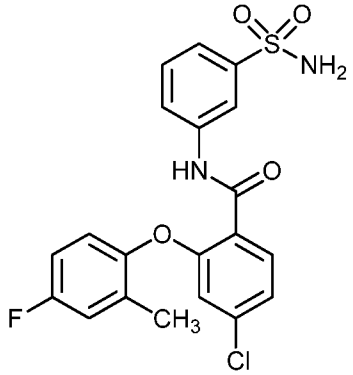
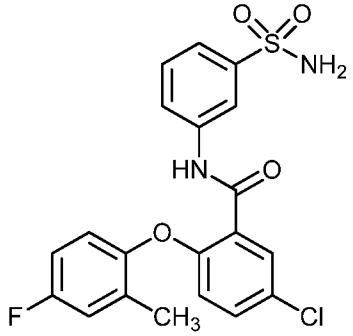
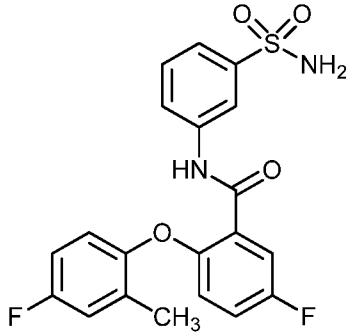
[0090] In another embodiment, the invention features a compound of formula I, wherein the compound or a pharmaceutically acceptable salt thereof, is selected from Table 1. Compounds names in Table 1 were generated using ChemBioDrawUltra version 12.0 from Cambridge Soft/Chem Office 2010.

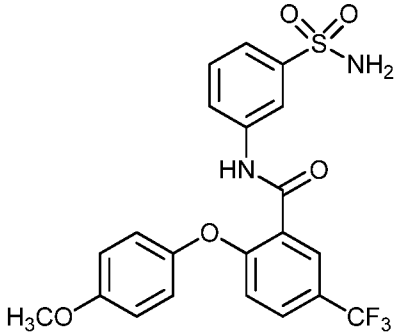
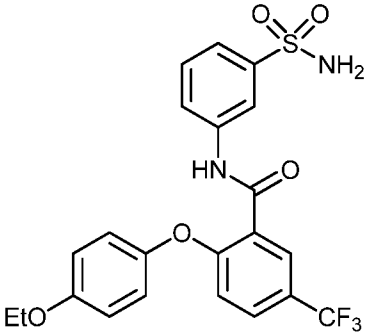
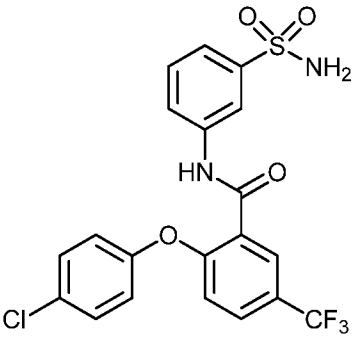
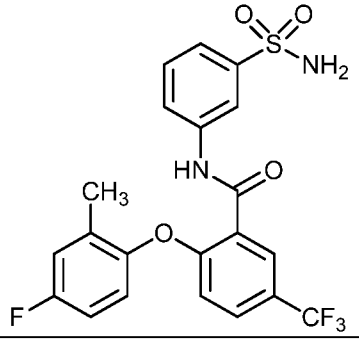
[0091] Table 1 Compound Numbers, Structures and Chemical Names

1	 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide
2	 2-(2,4-difluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide
3	 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide
4	 2-(2-chloro-4-fluorophenoxy)-4-cyano-N-(3-sulfamoylphenyl)benzamide
5	 5-chloro-2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide
6	 2-(2,4-difluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide

7	 4-chloro-2-(4-fluorophenoxy)-5-methyl-N-(3-sulfamoylphenyl)benzamide
8	 4-chloro-2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide
9	 4-cyano-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide
10	 4-cyano-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide
11	 2-(2-chloro-4-fluorophenoxy)-5-cyano-N-(3-sulfamoylphenyl)benzamide
12	 2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide

13	 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide
14	 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide
15	 4-chloro-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide
16	 5-chloro-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide
17	 5-chloro-2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide
18	 2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide

19	 4-chloro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide
20	 5-chloro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide
21	 5-fluoro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide

22	 2-(4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide
23	 2-(4-ethoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide
24	 2-(4-chlorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide
25	

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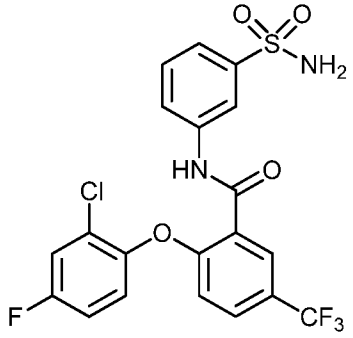
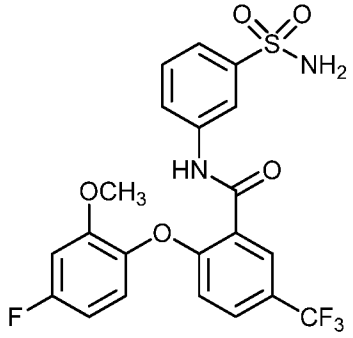
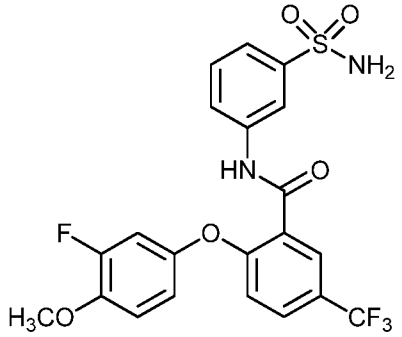
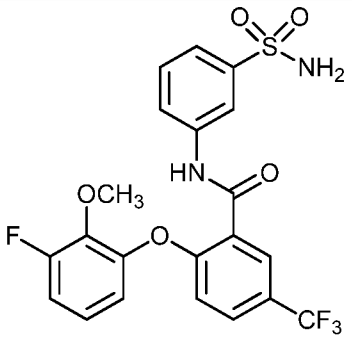
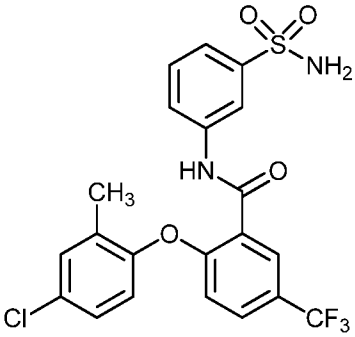
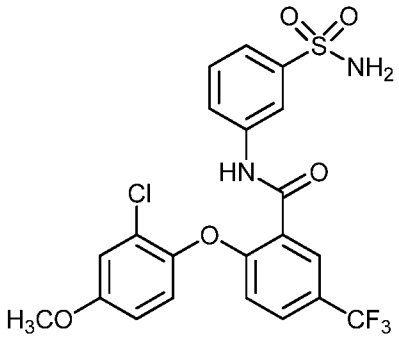
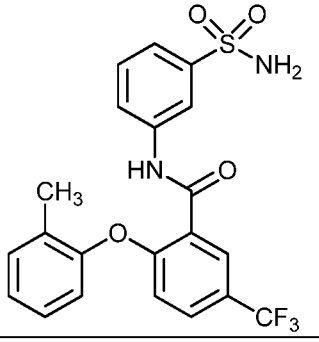
26	 2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide
27	 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide
28	 2-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide
29	 2-(3-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide
30	 2-(4-chloro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide
31	 2-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide
32	

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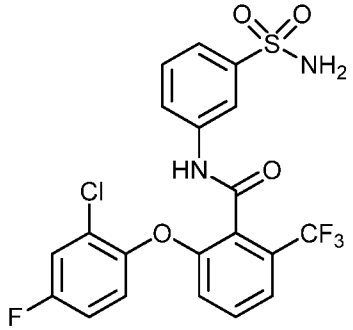
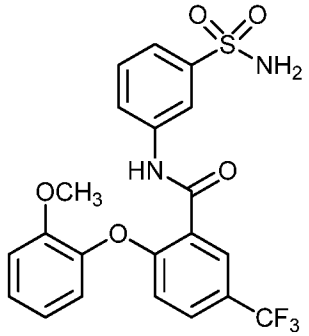
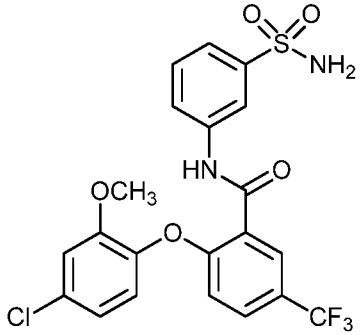
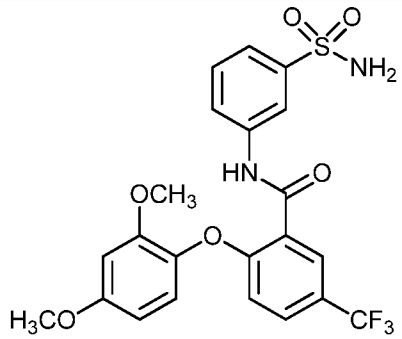
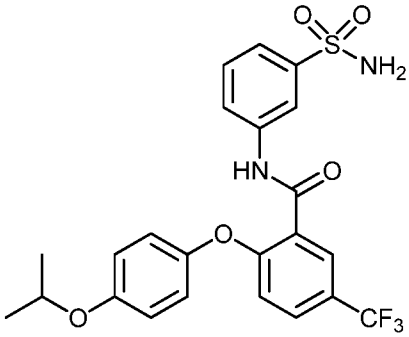
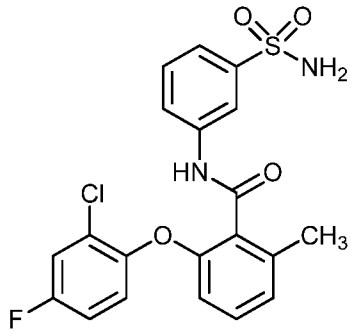
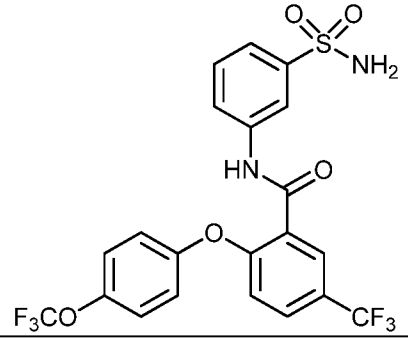
33	 2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide
34	 2-(2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide
35	 2-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide
36	 2-(2,4-dimethoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide
37	 2-(4-isopropoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide
38	 2-(2-chloro-4-fluorophenoxy)-6-methyl-N-(3-sulfamoylphenyl)benzamide
39	

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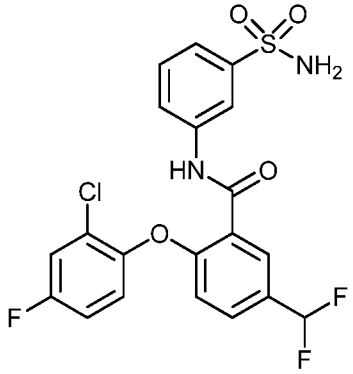
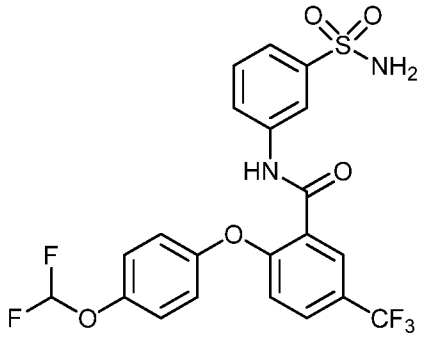
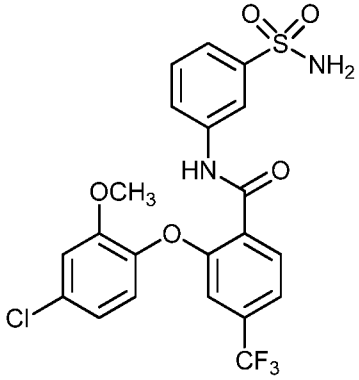
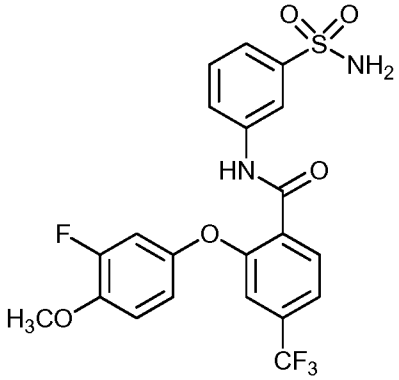
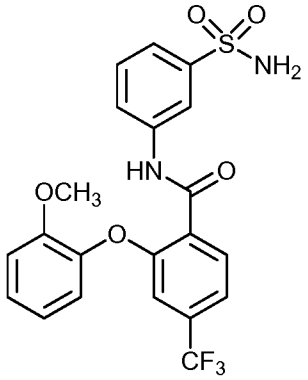
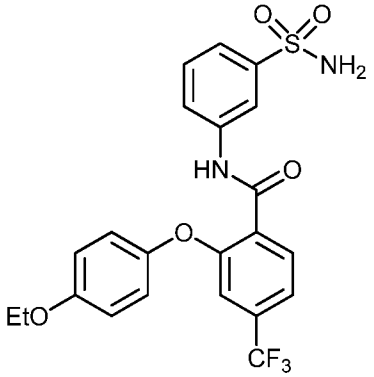
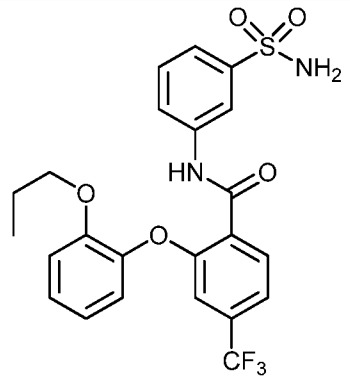
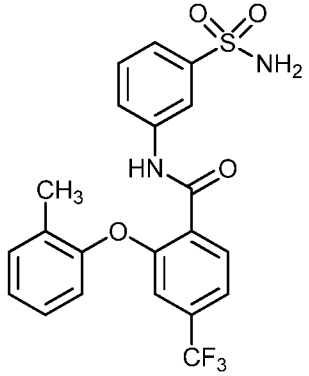
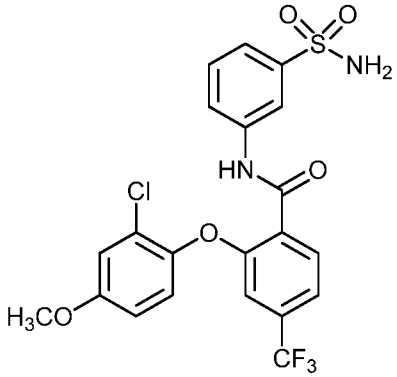
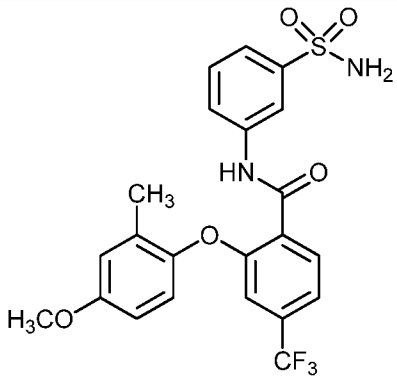
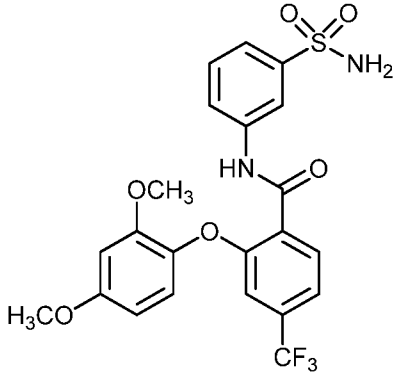
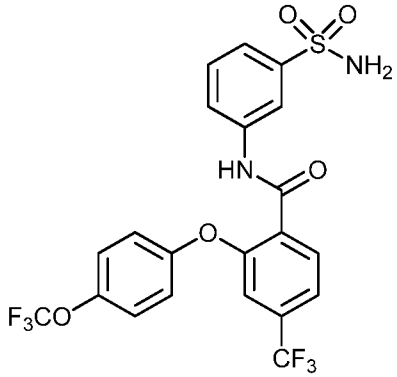
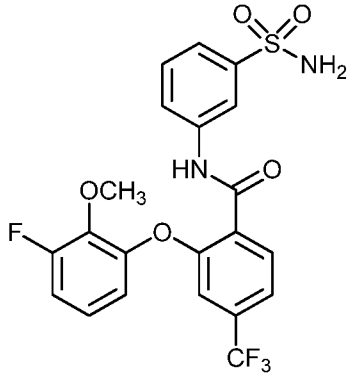
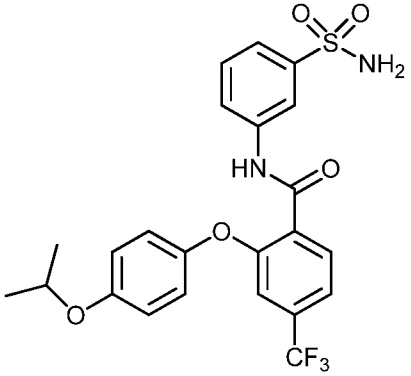
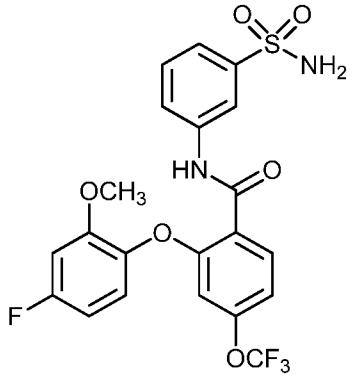
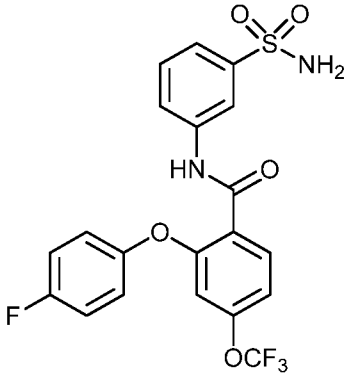
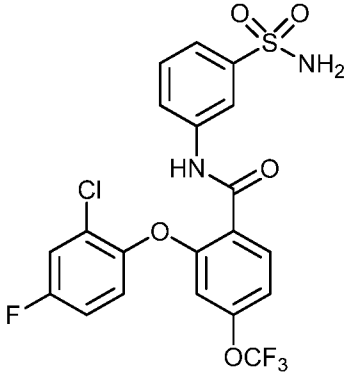
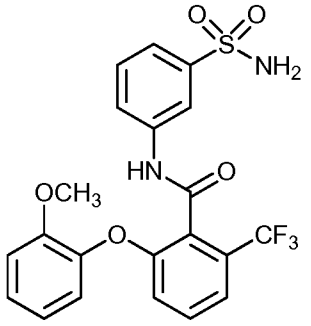
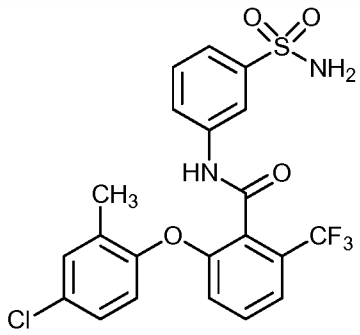
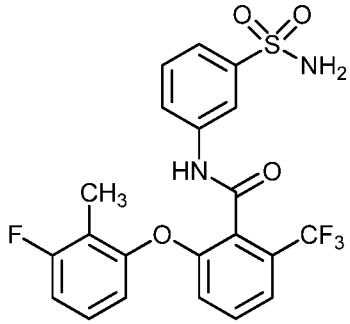
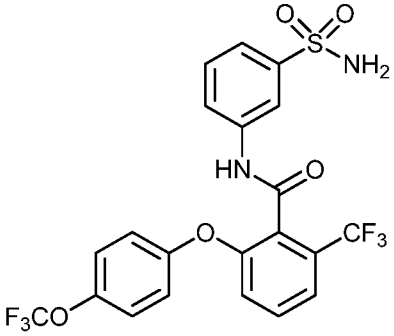
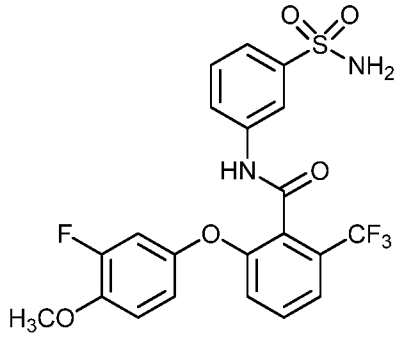
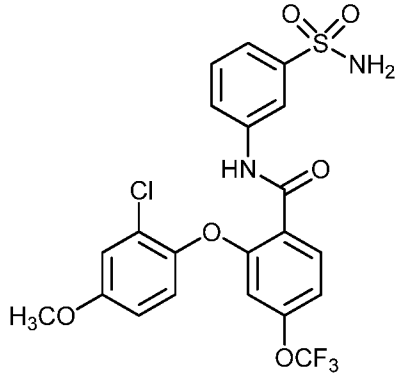
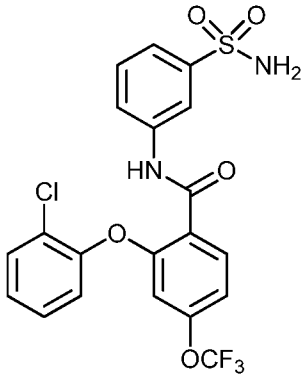
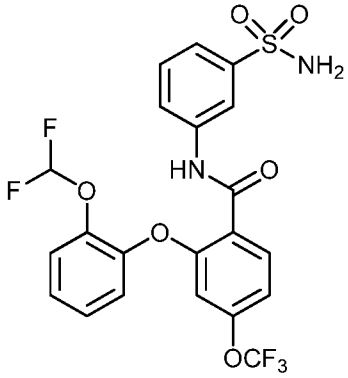
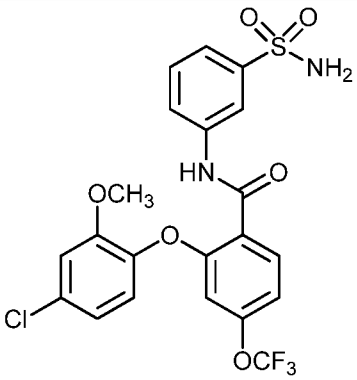
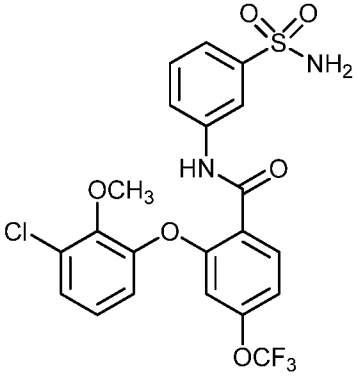
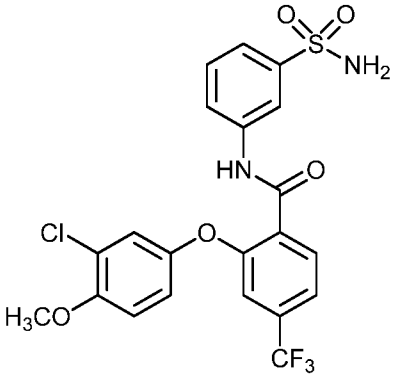
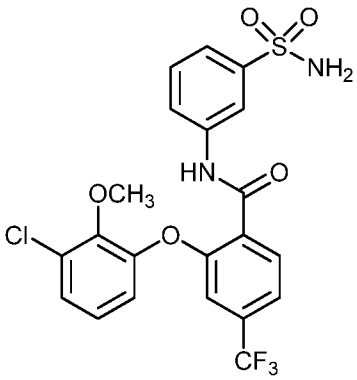
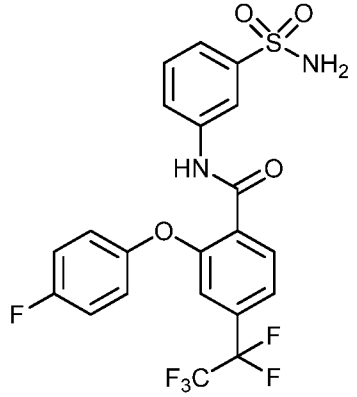
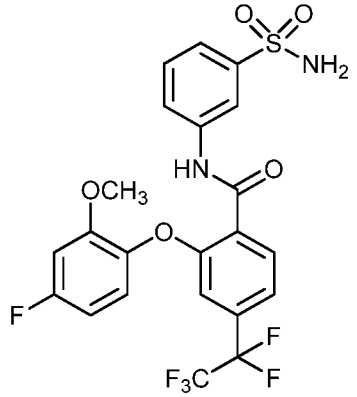
40	 2-(2-chloro-4-fluorophenoxy)-5-(difluoromethyl)-N-(3-sulfamoylphenyl)benzamide
41	 2-(4-(difluoromethoxy)phenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide
42	 2-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide
43	 2-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide
44	 2-(2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide
45	 2-(4-ethoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide

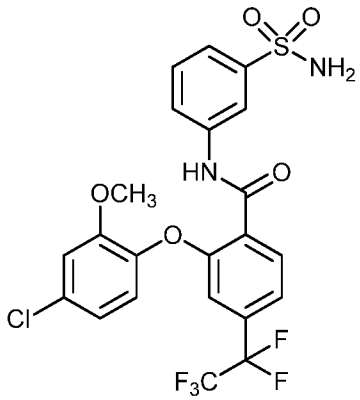
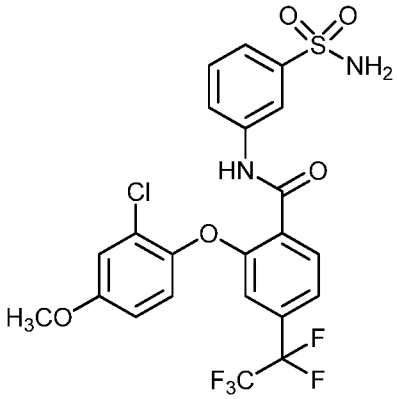
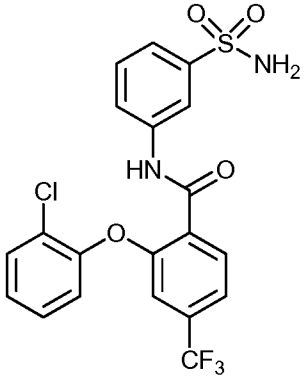
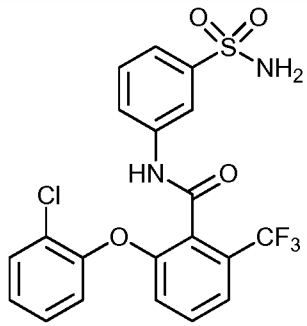
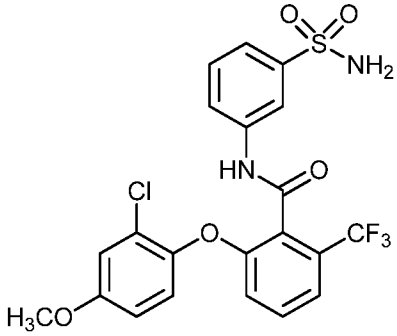
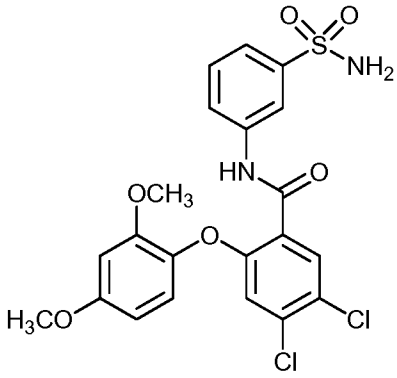
46	 2-(2-propoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide
47	 N-(3-sulfamoylphenyl)-2-(o-tolyloxy)-4-(trifluoromethyl)benzamide
48	 2-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide
49	 2-(4-methoxy-2-methylphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide
50	 2-(2,4-dimethoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide
51	 N-(3-sulfamoylphenyl)-2-(4-(trifluoromethoxy)phenoxy)-4-(trifluoromethyl)benzamide

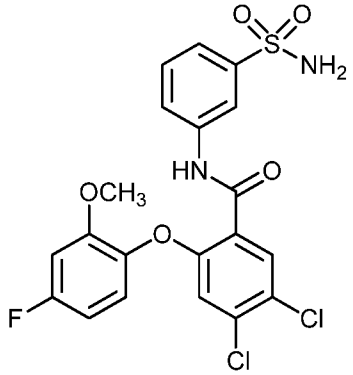
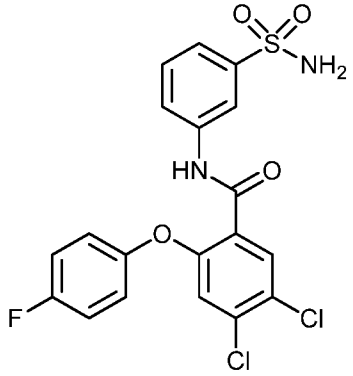
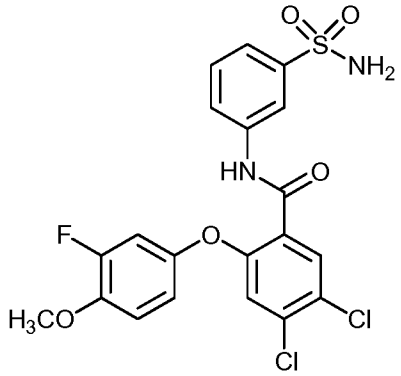
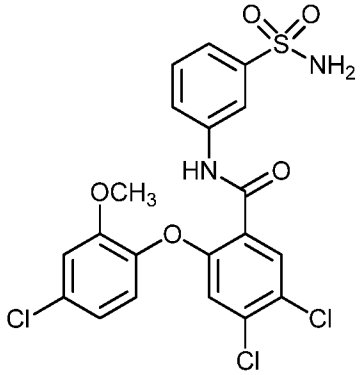
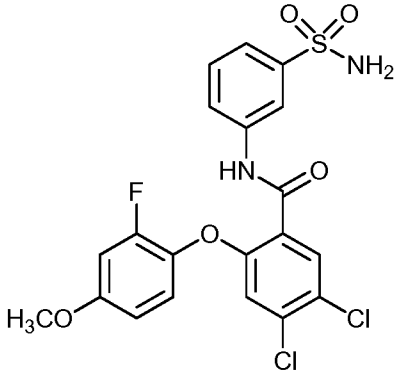
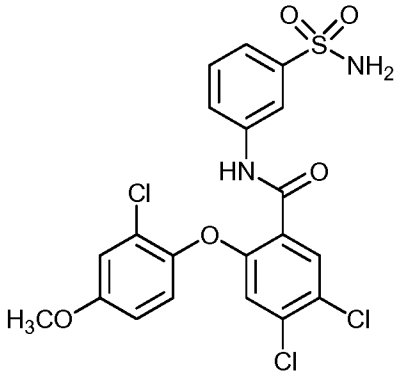
52	 2-(3-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide
53	 2-(4-isopropoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide
54	 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide
55	 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide
56	 2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide
57	 2-(2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide

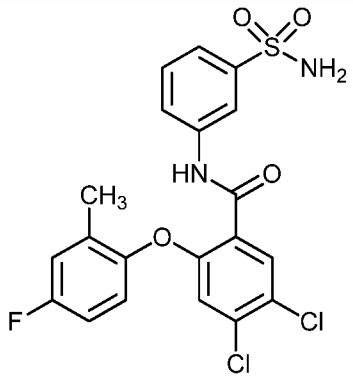
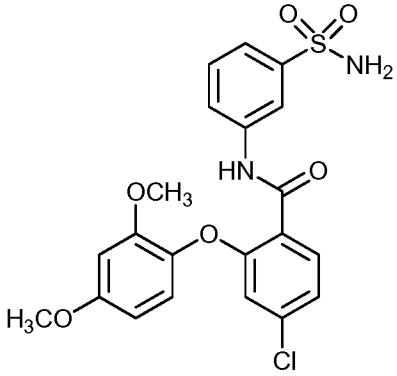
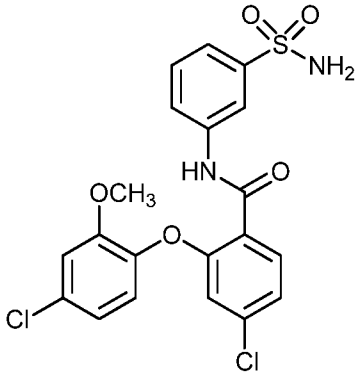
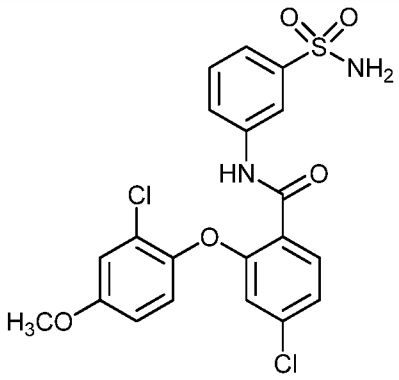
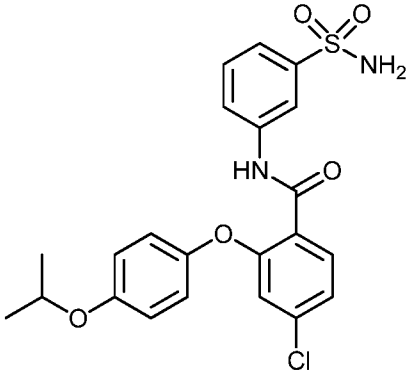
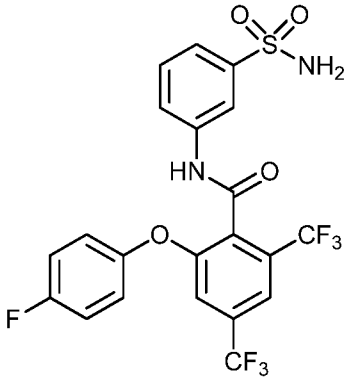
58	 2-(4-chloro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide
59	 2-(3-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide
60	 N-(3-sulfamoylphenyl)-2-(4-(trifluoromethoxy)phenoxy)-6-(trifluoromethyl)benzamide
61	 2-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide
62	 2-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide
63	 2-(2-chlorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide
64	 2-(2-(difluoromethoxy)phenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide

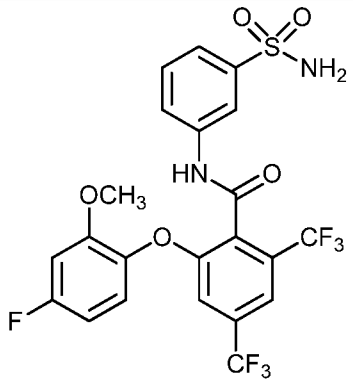
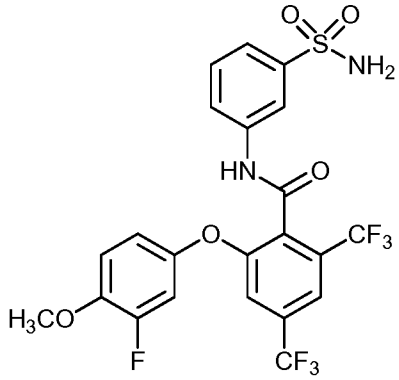
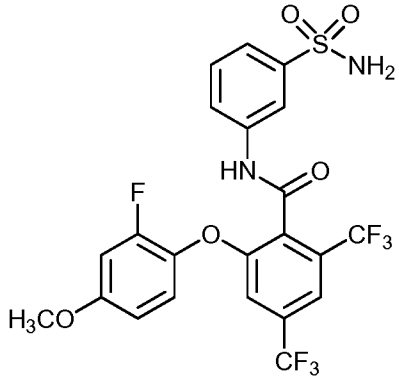
65	 2-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide
66	 2-(3-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide
67	 2-(3-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide

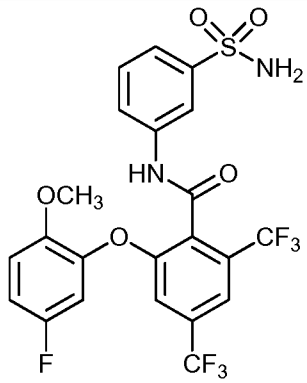
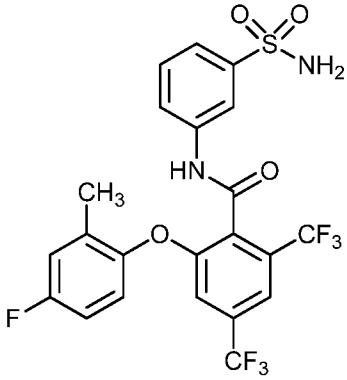
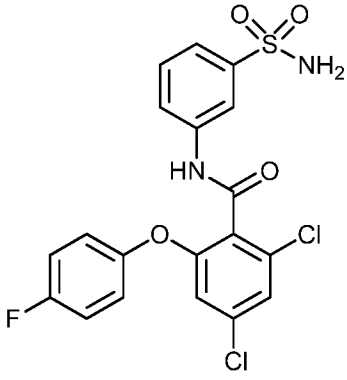
68	 2-(3-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide
69	 2-(4-fluorophenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide
70	 2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide

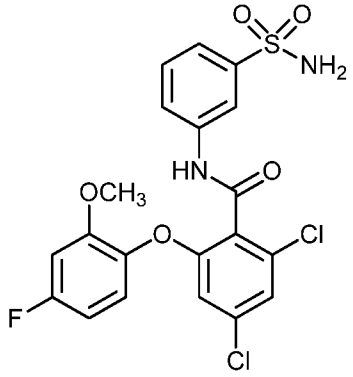
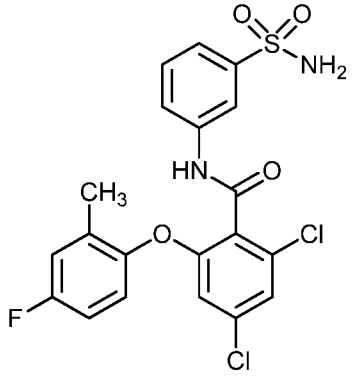
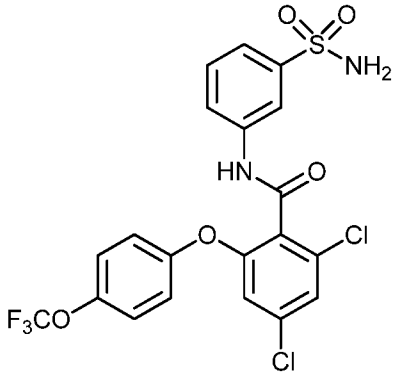
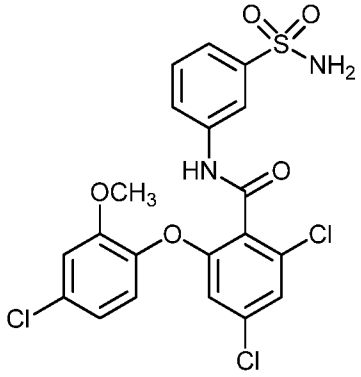
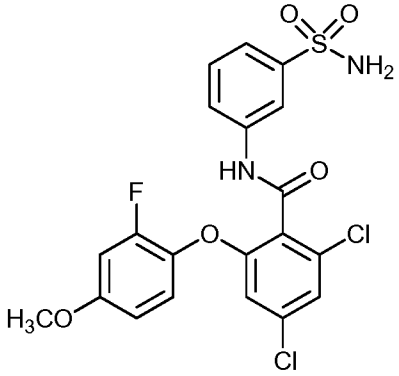
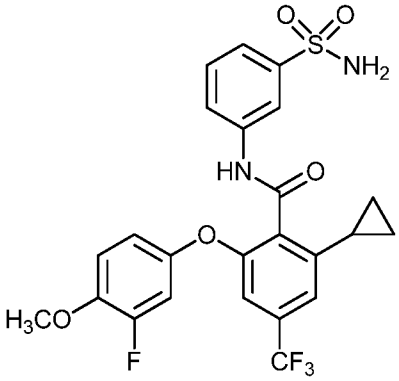
71	 2-(4-chloro-2-methoxyphenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide
72	 2-(2-chloro-4-methoxyphenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide
73	 2-(2-chlorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide
74	 2-(2-chlorophenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide
75	 2-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide
76	 4,5-dichloro-2-(2,4-dimethoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide

77	 4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide
78	 4,5-dichloro-2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide
79	 4,5-dichloro-2-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide
80	 4,5-dichloro-2-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide
81	 4,5-dichloro-2-(2-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide
82	 4,5-dichloro-2-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide

83	 4,5-dichloro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide
84	 4-chloro-2-(2,4-dimethoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide
85	 4-chloro-2-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide
86	 4-chloro-2-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide
87	 4-chloro-2-(4-isopropoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide
88	 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide

89	 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide
90	 2-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide
91	 2-(2-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide

92	 2-(5-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide
93	 2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide
94	 2,4-dichloro-6-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide

95	 2,4-dichloro-6-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide
96	 2,4-dichloro-6-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide
97	 2,4-dichloro-N-(3-sulfamoylphenyl)-6-(4-(trifluoromethoxy)phenoxy)benzamide
98	 2,4-dichloro-6-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide
99	 2,4-dichloro-6-(2-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide
100	 2-cyclopropyl-6-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide

[0092] In one embodiment, the compound is 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide or a pharmaceutically acceptable salt thereof.

[0093] In another embodiment, the compound is 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide or a pharmaceutically acceptable salt thereof.

[0094] In another embodiment, the compound is 2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide or a pharmaceutically acceptable salt thereof.

[0095] In another embodiment, the compound is 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide or a pharmaceutically acceptable salt thereof.

[0096] In another embodiment, the compound is 2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide or a pharmaceutically acceptable salt thereof.

[0097] In another embodiment, the compound is 2-(2-chloro-4-fluorophenoxy)-5-(difluoromethyl)-N-(3-sulfamoylphenyl)benzamide or a pharmaceutically acceptable salt thereof.

[0098] In another embodiment, the compound is 2-(4-fluorophenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide or a pharmaceutically acceptable salt thereof.

[0099] In another embodiment, the compound is 2-(4-chloro-2-methoxyphenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide or a pharmaceutically acceptable salt thereof.

[00100] In another embodiment, the compound is 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide or a pharmaceutically acceptable salt thereof.

[00101] In another embodiment, the compound is 5-chloro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide or a pharmaceutically acceptable salt thereof.

[00102] In another embodiment, the compound is 4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide or a pharmaceutically acceptable salt thereof.

[00103] In another embodiment, the compound is 2,4-dichloro-6-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide or a pharmaceutically acceptable salt thereof.

[00104] In another embodiment, the compound is 2,4-dichloro-6-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide or a pharmaceutically acceptable salt thereof.

[00105] In another embodiment, the compound is 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide or a pharmaceutically acceptable salt thereof.

[00106] In another embodiment, the compound is 2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide or a pharmaceutically acceptable salt thereof.

[00107] In another embodiment, the compound is 5-chloro-2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide or a pharmaceutically acceptable salt thereof.

[00108] In another embodiment, the compound is 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide or a pharmaceutically acceptable salt thereof.

[00109] In another embodiment, the compound is 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide or a pharmaceutically acceptable salt thereof.

[00110] In another embodiment, the compound is 4,5-dichloro-2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide or a pharmaceutically acceptable salt thereof.

[00111] In another embodiment, the compound is 2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide or a pharmaceutically acceptable salt thereof.

[00112] In another embodiment, the compound is 5-fluoro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide or a pharmaceutically acceptable salt thereof.

[00113] In another embodiment, the compound is 2-(2-chloro-4-fluorophenoxy)-4-cyano-N-(3-sulfamoylphenyl)benzamide or a pharmaceutically acceptable salt thereof.

[00114] In another embodiment, the compound is N-(3-sulfamoylphenyl)-2-(4-(trifluoromethoxy)phenoxy)-4-(trifluoromethyl)benzamide.

Salts, Compositions, Uses, Formulation,Administration and Additional Agents

Pharmaceutically acceptable salts and compositions

[00115] As discussed herein, the invention provides compounds that are inhibitors of voltage-gated sodium channels, and thus the present compounds are useful for the treatment of diseases, disorders, and conditions including, but not limited to chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence or cardiac arrhythmia. Accordingly, in another aspect of the invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents. In another embodiment, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of the compound of formula I or a pharmaceutically acceptable salt thereof of and one or more pharmaceutically acceptable carriers or vehicles.

[00116] It will also be appreciated that certain of the compounds of invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a subject in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[00117] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgement, suitable for use in contact

with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of a voltage-gated sodium channel.

[00118] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et *al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, **1977**, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}$ alkyl$)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium,

potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[00119] As described herein, the pharmaceutically acceptable compositions of the invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution;

ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[00120] In another aspect, the invention features a pharmaceutical composition comprising the compound of the invention and a pharmaceutically acceptable carrier.

[00121] In another aspect, the invention features a pharmaceutical composition comprising a therapeutically effective amount of the compound or a pharmaceutically acceptable salt thereof of the compounds of formula I and one or more pharmaceutically acceptable carriers or vehicles.

Uses of Compounds and Pharmaceutically Acceptable Salts and Compositions

[00122] In another aspect, the invention features a method of inhibiting a voltage-gated sodium channel in a subject comprising administering to the subject a compound of formula I or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof. In another aspect, the voltage-gated sodium channel is Nav1.8.

[00123] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence or cardiac arrhythmia comprising administering an effective amount of a compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula I.

[00124] In another aspect, the invention features a method of treating or lessening the severity in a subject of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence or cardiac arrhythmia comprising administering an effective amount of a compound or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula I.

[00125] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of gut pain wherein gut pain comprises inflammatory bowel disease pain, Crohn's disease pain or interstitial cystitis pain.

[00126] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of neuropathic pain wherein neuropathic pain comprises post-herpetic neuralgia, diabetic neuralgia, painful HIV-associated sensory neuropathy, trigeminal neuralgia, burning mouth syndrome, post-amputation pain, phantom pain, painful neuroma; traumatic neuroma; Morton's neuroma; nerve entrapment injury, spinal stenosis, carpal tunnel syndrome, radicular pain, sciatica pain; nerve avulsion injury, brachial plexus avulsion injury; complex regional pain syndrome, drug therapy induced neuralgia, cancer chemotherapy induced neuralgia, anti-retroviral therapy induced neuralgia; post spinal cord injury pain, idiopathic small-fiber neuropathy, idiopathic sensory neuropathy or trigeminal autonomic cephalalgia.

[00127] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of musculoskeletal pain wherein musculoskeletal pain comprises osteoarthritis pain, back pain, cold pain, burn pain or dental pain.

[00128] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of idiopathic pain wherein idiopathic pain comprises fibromyalgia pain.

[00129] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of inflammatory pain wherein inflammatory pain comprises rheumatoid arthritis pain or vulvodynia.

[00130] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence or cardiac arrhythmia comprising administering an effective amount of a compound or a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula I with one or more additional

therapeutic agents administered concurrently with, prior to, or subsequent to treatment with the compound or pharmaceutical composition.

[00131] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of gut pain, wherein gut pain comprises inflammatory bowel disease pain, Crohn's disease pain or interstitial cystitis pain wherein said method comprises administering an effective amount of a compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula I.

[00132] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of neuropathic pain, wherein neuropathic pain comprises post-herpetic neuralgia, diabetic neuralgia, painful HIV-associated sensory neuropathy, trigeminal neuralgia, burning mouth syndrome, post-amputation pain, phantom pain, painful neuroma, traumatic neuroma, Morton's neuroma; nerve entrapment injury, spinal stenosis, carpal tunnel syndrome, radicular pain, sciatica pain; nerve avulsion injury, brachial plexus avulsion injury; complex regional pain syndrome, drug therapy induced neuralgia, cancer chemotherapy induced neuralgia, anti-retroviral therapy induced neuralgia; post spinal cord injury pain, idiopathic small-fiber neuropathy, idiopathic sensory neuropathy or trigeminal autonomic cephalalgia wherein said method comprises administering an effective amount of a compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula I.

[00133] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of musculoskeletal pain, wherein musculoskeletal pain comprises osteoarthritis pain, back pain, cold pain, burn pain or dental pain wherein said method comprises administering an effective amount of a compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula I.

[00134] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of inflammatory pain, wherein inflammatory pain comprises rheumatoid arthritis pain or vulvodynia wherein said method comprises administering an effective amount of a compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula I.

[00135] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of idiopathic pain, wherein idiopathic pain comprises fibromyalgia pain wherein said method comprises administering an effective amount of a compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula I.

[00136] In yet another aspect, the invention features a method wherein the subject is treated with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with an effective amount of a compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula I.

[00137] In another aspect, the invention features a method of inhibiting a voltage-gated sodium channel in a subject comprising administering to the subject an effective amount of a compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula I. In another aspect, the voltage-gated sodium channel is Nav1.8.

[00138] In another aspect, the invention features a method of inhibiting a voltage-gated sodium channel in a biological sample comprising contacting the biological sample with an effective amount of a compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula I. In another aspect, the voltage-gated sodium channel is Nav1.8.

[00139] In another aspect, the invention features a method of treating or lessening the severity in a subject of acute pain, chronic pain, neuropathic pain, inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy, epilepsy conditions, neurodegenerative disorders, psychiatric disorders, anxiety, depression, dipolar disorder, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head pain, neck pain, severe pain, intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, cancer pain, stroke, cerebral ischemia, traumatic brain injury, amyotrophic lateral sclerosis, stress induced angina, exercise induced angina,

palpitations, hypertension, or abnormal gastro-intestinal motility, comprising administering an effective amount of a compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula I.

[00140] In another aspect, the invention features a method of treating or lessening the severity in a subject of femur cancer pain; non-malignant chronic bone pain; rheumatoid arthritis; osteoarthritis; spinal stenosis; neuropathic low back pain; myofascial pain syndrome; fibromyalgia; temporomandibular joint pain; chronic visceral pain, abdominal pain; pancreatic pain; IBS pain; chronic and acute headache pain; migraine; tension headache, cluster headaches; chronic and acute neuropathic pain, post-herpetic neuralgia; diabetic neuropathy; HIV-associated neuropathy; trigeminal neuralgia; Charcot-Marie Tooth neuropathy; hereditary sensory neuropathies; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; complex regional pain syndrome; phantom pain; intractable pain; acute pain, acute post-operative pain; acute musculoskeletal pain; joint pain; mechanical low back pain; neck pain; tendonitis; injury pain; exercise pain; acute visceral pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; chest pain, cardiac pain; pelvic pain, renal colic pain, acute obstetric pain, labor pain; cesarean section pain; acute inflammatory, burn and trauma pain; acute intermittent pain, endometriosis; acute herpes zoster pain; sickle cell anemia; acute pancreatitis; breakthrough pain; orofacial pain including sinusitis pain, dental pain; multiple sclerosis (MS) pain; pain in depression; leprosy pain; Behcet's disease pain; adiposis dolorosa; phlebitic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; erythromelalgia pain; Fabry's disease pain; bladder and urogenital disease, including, urinary incontinence; hyperactivity bladder; painful bladder syndrome; interstitial cyctitis (IC); prostatitis; complex regional pain syndrome (CRPS), type I and type II; widespread pain, paroxysmal extreme pain, pruritis, tinnitis, or angina-induced pain, comprising administering an effective amount of a compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula I.

[00141] In another aspect, the invention features a method of treating or lessening the severity in a subject of neuropathic pain comprising administering an effective

amount of a compound, a pharmaceutically acceptable salt thereof or a pharmaceutical composition of the compounds of formula I. In one aspect, the neuropathic pain is selected from post-herpetic neuralgia, diabetic neuralgia, painful HIV-associated sensory neuropathy, trigeminal neuralgia, burning mouth syndrome, post-amputation pain, phantom pain, painful neuroma, traumatic neuroma, Morton's neuroma, nerve entrapment injury, spinal stenosis, carpal tunnel syndrome, radicular pain, sciatica pain, nerve avulsion injury, brachial plexus avulsion, complex regional pain syndrome, drug therapy induced neuralgia, cancer chemotherapy induced neuralgia, anti-retroviral therapy induced neuralgia, post spinal cord injury pain, idiopathic small-fiber neuropathy, idiopathic sensory neuropathy or trigeminal autonomic cephalalgia.

Manufacture of Medicaments

[00142] In one aspect, the invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament for use in inhibiting a voltage-gated sodium channel. In another aspect, the voltage-gated sodium channel is Nav1.8.

[00143] In yet another aspect, the invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament for use in treating or lessening the severity in a subject of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence or cardiac arrhythmia.

[00144] In yet another aspect, the invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament for use in treating or lessening the severity in a subject of gut pain, wherein gut pain comprises inflammatory bowel disease pain, Crohn's disease pain or interstitial cystitis pain.

[00145] In yet another aspect, the invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament for use in a treating or lessening the severity in a subject of neuropathic pain, wherein neuropathic pain comprises post-herpetic neuralgia, diabetic neuralgia, painful HIV-associated sensory neuropathy, trigeminal neuralgia, burning mouth syndrome, post-amputation pain, phantom

pain, painful neuroma, traumatic neuroma, Morton's neuroma; nerve entrapment injury, spinal stenosis, carpal tunnel syndrome, radicular pain, sciatica pain; nerve avulsion injury, brachial plexus avulsion injury; complex regional pain syndrome, drug therapy induced neuralgia, cancer chemotherapy induced neuralgia, anti-retroviral therapy induced neuralgia; post spinal cord injury pain, idiopathic small-fiber neuropathy, idiopathic sensory neuropathy or trigeminal autonomic cephalalgia.

[00146] In yet another aspect, the invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament for use in treating or lessening the severity in a subject of musculoskeletal pain, wherein musculoskeletal pain comprises osteoarthritis pain, back pain, cold pain, burn pain or dental pain.

[00147] In yet another aspect, the invention the invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament for use in treating or lessening the severity in a subject of inflammatory pain, wherein inflammatory pain comprises rheumatoid arthritis pain or vulvodynia.

[00148] In yet another aspect, the invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament for use in treating or lessening the severity in a subject of idiopathic pain, wherein idiopathic pain comprises fibromyalgia pain.

[00149] In yet another aspect, the invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament in combination with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with the compound or pharmaceutical composition.

[00150] In another aspect, the invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament for use in treating or lessening the severity of acute pain, chronic pain, neuropathic pain, inflammatory pain, arthritis, migraine, cluster headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy, epilepsy conditions, neurodegenerative disorders, psychiatric disorders, anxiety, depression, dipolar disorder, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, multiple sclerosis, irritable bowel syndrome, incontinence,

visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, head pain, neck pain, severe pain, intractable pain, nociceptive pain, breakthrough pain, postsurgical pain, cancer pain, stroke, cerebral ischemia, traumatic brain injury, amyotrophic lateral sclerosis, stress induced angina, exercise induced angina, palpitations, hypertension, or abnormal gastro-intestinal motility.

[00151] In another aspect, the invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament for use in treating or lessening the severity of femur cancer pain; non-malignant chronic bone pain; rheumatoid arthritis; osteoarthritis; spinal stenosis; neuropathic low back pain; myofascial pain syndrome; fibromyalgia; temporomandibular joint pain; chronic visceral pain, abdominal pain; pancreatic pain; IBS pain; chronic and acute headache pain; migraine; tension headache, including, cluster headaches; chronic and acute neuropathic pain, post-herpetic neuralgia; diabetic neuropathy; HIV-associated neuropathy; trigeminal neuralgia; Charcot-Marie Tooth neuropathy; hereditary sensory neuropathies; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; complex regional pain syndrome; phantom pain; intractable pain; acute pain, acute post-operative pain; acute musculoskeletal pain; joint pain; mechanical low back pain; neck pain; tendonitis; injury/exercise pain; acute visceral pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; chest pain, cardiac pain; pelvic pain, renal colic pain, acute obstetric pain, labor pain; cesarean section pain; acute inflammatory, burn and trauma pain; acute intermittent pain, endometriosis; acute herpes zoster pain; sickle cell anemia; acute pancreatitis; breakthrough pain; orofacial pain including sinusitis pain, dental pain; multiple sclerosis (MS) pain; pain in depression; leprosy pain; Behcet's disease pain; adiposis dolorosa; phlebitic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; erythromelalgia pain; Fabry's disease pain; bladder and urogenital disease, including, urinary incontinence; hyperactivity bladder; painful bladder syndrome; interstitial cyctitis (IC); prostatitis; complex regional pain syndrome (CRPS), type I and type II; widespread pain, paroxysmal extreme pain, pruritis, tinnitis, or angina-induced pain.

[00152] In another aspect, the invention provides the use of a compound or pharmaceutical composition described herein for the manufacture of a medicament for use in treating or lessening the severity of neuropathic pain. In one aspect, the neuropathic pain is selected from post-herpetic neuralgia, diabetic neuralgia, painful HIV-associated sensory neuropathy, trigeminal neuralgia, burning mouth syndrome, post-amputation pain, phantom pain, painful neuroma, traumatic neuroma, Morton's neuroma, nerve entrapment injury, spinal stenosis, carpal tunnel syndrome, radicular pain, sciatica pain, nerve avulsion injury, brachial plexus avulsion, complex regional pain syndrome, drug therapy induced neuralgia, cancer chemotherapy induced neuralgia, anti-retroviral therapy induced neuralgia, post spinal cord injury pain, idiopathic small-fiber neuropathy, idiopathic sensory neuropathy or trigeminal autonomic cephalalgia.

Administration of Pharmaceutically Acceptable Salts and Compositions

[00153] In certain embodiments of the invention an "effective amount" of the compound, a pharmaceutically acceptable salt thereof or pharmaceutically acceptable composition is that amount effective for treating or lessening the severity of one or more of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence or cardiac arrhythmia.

[00154] The compounds and compositions, according to the method of the invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of one or more of the pain or non-pain diseases recited herein. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the subject to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular subject or organism will depend upon a variety of factors including the disorder

being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "subject" or "patient," as used herein, means an animal, preferably a mammal, and most preferably a human.

[00155] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00156] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00157] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally

acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally 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 are used in the preparation of injectables.

[00158] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00159] In order to prolong the effect of a compound of the invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00160] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00161] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with

at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00162] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00163] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of

capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00164] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms are prepared by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00165] As described generally above, the compounds of the invention are useful as inhibitors of voltage-gated sodium channels. In one embodiment, the compounds and compositions of the invention are inhibitors of $Na_V1.8$ and thus, without wishing to be bound by any particular theory, the compounds and compositions are particularly useful for treating or lessening the severity of a disease, condition, or disorder where activation or hyperactivity of $Na_V1.8$ is implicated in the disease, condition, or disorder. When activation or hyperactivity of $Na_V1.8$ is implicated in a particular disease, condition, or disorder, the disease, condition, or disorder may also be referred to as a "$Na_V1.8$ -mediated disease, condition or disorder." Accordingly, in another aspect, the invention provides a method for treating or lessening the severity of a disease, condition, or disorder where activation or hyperactivity of $Na_V1.8$ is implicated in the disease state.

[00166] The activity of a compound utilized in this invention as an inhibitor of $Na_V1.8$ may be assayed according to methods described generally in the Examples herein, or according to methods available to one of ordinary skill in the art.

Additional Therapeutic Agents

[00167] It will also be appreciated that the compounds and pharmaceutically acceptable compositions of the invention can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. In one embodiment, the subject is treated with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with the compound or pharmaceutical composition of formula I of the present invention. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated." For example, exemplary additional therapeutic agents include, but are not limited to: nonopioid analgesics (indoles such as Etodolac, Indomethacin, Sulindac, Tolmetin; naphthylalkanones such sa Nabumetone; oxicams such as Piroxicam; para-aminophenol derivatives, such as Acetaminophen; propionic acids such as Fenoprofen, Flurbiprofen, Ibuprofen, Ketoprofen, Naproxen, Naproxen sodium, Oxaprozin; salicylates such as Aspirin, Choline magnesium trisalicylate, Diflunisal; fenamates such as meclofenamic acid, Mefenamic acid; and pyrazoles such as Phenylbutazone); or opioid (narcotic) agonists (such as Codeine, Fentanyl, Hydromorphone, Levorphanol, Meperidine, Methadone, Morphine, Oxycodone, Oxymorphone, Propoxyphene, Buprenorphine, Butorphanol, Dezocine, Nalbuphine, and Pentazocine). Additionally, nondrug analgesic approaches may be utilized in conjunction with administration of one or more compounds of the invention. For example, anesthesiologic (intraspinal infusion, neural blockade), neurosurgical (neurolysis of CNS pathways), neurostimulatory (transcutaneous electrical nerve stimulation, dorsal column stimulation), physiatric (physical therapy, orthotic devices, diathermy), or psychologic

(cognitive methods-hypnosis, biofeedback, or behavioral methods) approaches may also be utilized. Additional appropriate therapeutic agents or approaches are described generally in The Merck Manual, Nineteenth Edition, Ed. Robert S. Porter and Justin L. Kaplan, Merck Sharp &Dohme Corp., a subsidiary of Merck & Co., Inc., 2011, and the Food and Drug Administration website, www.fda.gov, the entire contents of which are hereby incorporated by reference.

[00168] In another embodiment, the additional therapeutic agent is an Na_V 1.7 inhibitor. Na_V 1.7 and Na_V 1.8 ion channels are both highly expressed in the sensory neurons of the dorsal root ganglion, where pain signals originate, but the distinct functional behavior of the two channels leads them to fulfill distinct and complementary roles in neuronal excitability. $Na_V1.7$ controls the general sensitivity of nociceptive neurons, and initiating the painful signal in a nociceptor. $Na_V1.8$ amplifies and sustains the pain signal once it has been initiated. Because of these distinct roles, inhibiting both channels should increase the effectiveness of pain relief. Preclinical genetic knockout mice support this idea, as double knockouts of $Na_V1.7$ and $Na_V1.8$ channels in the sensory DRG neurons surprisingly diminish nociceptive behaviors to a greater degree than knockout of either channel alone.

[00169] In another embodiment, additional appropriate therapeutic agents are selected from the following:

[00170] (1) an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine;

[00171] (2) a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflunisal, 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 or zomepirac;

[00172] (3) a barbiturate sedative, e.g. amobarbital, aprobarbital, butabarbital, butalbital, mephobarbital, metharbital, methohexital, pentobarbital, phenobarbital,

secobarbital, talbutal, thiamylal or thiopental;

[00173] (4) a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;

[00174] (5) a histamine (H_1) antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;

[00175] (6) a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone;

[00176] (7) a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphenadrine;

[00177] (8) an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N- methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinine, cis-4-(phosphonomethyl)-2- piperidinecarboxylic acid, budipine, EN-3231 (MorphiDex®), a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perzinfotel including an NR2B antagonist, e.g. ifenprodil, traxoprodil or (-)-(R)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-l- piperidinyl]-l-hydroxyethyl-3,4-dihydro-2(lH)-quinolinone;

[00178] (9) an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmedetomidine, modafinil, or 4-amino-6,7-dimethoxy-2-(5-methane-sulfonamido-l, 2,3,4- tetrahydroisoquinolin-2-yl)-5-(2-pyridyl) quinazoline;

[00179] (10) a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline;

[00180] (11) an anticonvulsant, e.g. carbamazepine (Tegretol®), lamotrigine, topiramate, lacosamide (Vimpat®) or valproate;

[00181] (12) a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (alphaR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11 -tetrahydro-9-methyl-5-(4- methylphenyl)-7H-[l,4]diazocino[2,l-g][l,7]-naphthyridine-6-13-dione (TAK-637), 5- [[(2R,3S)-2-[(lR)-l-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-l,2-dihydro-3H-l,2,4-triazol-3-one (MK-869), aprepitant, lanepitant,

dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);

[00182] (13) a muscarinic antagonist, e.g oxybutynin, tolterodine, propiverine, tropsium chloride, darifenacin, solifenacin, temiverine and ipratropium;

[00183] (14) a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib;

[00184] (15) a coal-tar analgesic, in particular paracetamol;

[00185] (16) a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonepiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, balaperidone, palindore, eplivanserin, osanetant, rimonabant, meclinertant, Miraxion® or sarizotan;

[00186] (17) a vanilloid receptor agonist (e.g. resinferatoxin or civamide) or antagonist (e.g. capsazepine, GRC-15300);

[00187] (18) a beta-adrenergic such as propranolol;

[00188] (19) a local anaesthetic such as mexiletine;

[00189] (20) a corticosteroid such as dexamethasone;

[00190] (21) a 5-HT receptor agonist or antagonist, particularly a 5-$HT_{1B/1D}$ agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;

[00191] (22) a 5-HT_{2A} receptor antagonist such as R(+)-alpha-(2,3-dimethoxy-phenyl)-l-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (MDL-100907);

[00192] (23) a cholinergic (nicotinic) analgesic, such as ispronicline (TC-1734), (E)-N-methyl-4-(3-pyridinyl)-3-buten-l-amine (RJR-2403), (R)-5-(2-azetidinylmethoxy)-2-chloropyridine (ABT-594) or nicotine;

[00193] (24) Tramadol, Tramadol ER (Ultram ER®), Tapentadol ER (Nucynta®);

[00194] (25) a PDE5 inhibitor, such as 5-[2-ethoxy-5-(4-methyl-l-piperazinyl-sulphonyl)phenyl]-l-methyl-3-n-propyl-l,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), (6R,12aR)- 2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',l':6,l]-pyrido[3,4-b]indole-l,4-dione (IC-351 or tadalafil), 2-[2-ethoxy-5-(4-ethyl-piperazin-l-yl-l-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,l-f][l,2,4]triazin-4-one (vardenafil), 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(l-ethyl-3-azetidinyl)-2,6-dihydro-7*H*- pyrazolo[4,3-*d*]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(l-isopropyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-[2-ethoxy-5-(4-ethylpiperazin-l-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-l-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide, 3-(l-methyl-7-oxo-3-propyl-6,7-dihydro-lH-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(l-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;

[00195] (26) an alpha-2-delta ligand such as gabapentin (Neurontin®), gabapentin GR (Gralise®), gabapentin, enacarbil (Horizant®), pregabalin (Lyrica®), 3-methyl gabapentin, (l[alpha],3[alpha],5[alpha])(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (2S,4S)-4-(3-chlorophenoxy)proline, (2S,4S)-4-(3-fluorobenzyl)-proline, [(lR,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(l-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(l-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-heptanoic acid and (3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid;

[00196] (27) a cannabinoid such as KHK-6188;

[00197] (28) metabotropic glutamate subtype 1 receptor (mGluRl) antagonist;

[00198] (29) a serotonin reuptake inhibitor such as sertraline, sertraline metabolite demethylsertraline, fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram,

escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, ericlamine and trazodone;

[00199] (30) a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, bupropion, bupropion metabolite hydroxybupoprion, nomifensine and viloxazine (Vivalan®), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (S,S)-reboxetine;

[00200] (31) a dual serotonin-noradrenaline reuptake inhibitor, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine (Cymbalta®), milnacipran and imipramine;

[00201] (32) an inducible nitric oxide synthase (iNOS) inhibitor such as S-[2-[(1-iminoethyl)amino]ethyl]-L-homocysteine, S-[2-[(1-iminoethyl)-amino]ethyl]-4,4-dioxo-L-cysteine, S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-L-cysteine, (2S,5Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-5-heptenoic acid, 2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)-butyl]thio]-S-chloro-S-pyridinecarbonitrile; 2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chlorobenzonitrile, (2S,4R)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol, 2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl) butyl]thio]-6-(trifluoromethyl)-3-pyridinecarbonitrile, 2-[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chlorobenzonitrile, N-[4-[2-(3-chlorobenzylamino)ethyl]phenyl]thiophene-2-carboxamidine, NXN-462, or guanidinoethyldisulfide;

[00202] (33) an acetylcholinesterase inhibitor such as donepezil;

[00203] (34) a prostaglandin E2 subtype 4 (EP4) antagonist such as *N*-[({2-[4-(2-ethyl-4,6- dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl}amino)-carbonyl]-4-methylbenzenesulfonamide or 4-[(15)-1-({[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;

[00204] (35) a leukotriene B4 antagonist; such as 1-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid (CP- 105696), 5-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-5E-hexenyl]oxyphenoxy]-valeric acid (ONO-4057) or DPC-11870;

[00205] (36) a 5-lipoxygenase inhibitor, such as zileuton, 6-[(3-fluoro-5-[4-methoxy-3,4,5,6- tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-l-methyl-2-quinolone (ZD-2138), or 2,3,5- trimethyl-6-(3-pyridylmethyl)-l,4-benzoquinone (CV-6504);

[00206] (37) a sodium channel blocker, such as lidocaine, lidocaine plus tetracaine cream (ZRS-201) or eslicarbazepine acetate;

[00207] (38) an $Na_V1.7$ blocker, such as XEN-402 and such as those disclosed in WO2011/140425; WO2012/106499; WO2012/112743; WO2012/125613; WO2013067248 or PCT/US2013/21535 the entire contents of each application hereby incorporated by reference.

[00208] (39) an $Na_V1.8$ blocker, such as those disclosed in WO2008/135826 and WO2006/011050 the entire contents of each application hereby incorporated by reference.

[00209] (40) a combined $Na_V1.7$ and $Na_V1.8$ blocker, such as DSP-2230 or BL-1021;

[00210] (41) a 5-HT3 antagonist, such as ondansetron;

[00211] (42) a TPRV 1 receptor agonist, such as capsaicin (NeurogesX®, Qutenza®); and the pharmaceutically acceptable salts and solvates thereof;

[00212] (43) a nicotinic receptor antagonist, such as varenicline;

[00213] (44) an N-type calcium channel antagonist, such as Z-160;

[00214] (45) a nerve growth factor antagonist, such as tanezumab;

[00215] (46) an endopeptidase stimulant, such as senrebotase;

[00216] (47) an angiotensin II antagonist, such as EMA-401;

[00217] In one embodiment, the additional appropriate therapeutic agents are selected from V-116517, Pregabalin, controlled release Pregabalin, Ezogabine (Potiga®). Ketamine/amitriptyline topical cream (Amiket®), AVP-923, Perampanel (E-2007), Ralfinamide, transdermal bupivacaine (Eladur®), CNV1014802, JNJ-10234094 (Carisbamate), BMS-954561or ARC-4558.

[00218] The amount of additional therapeutic agent present in the compositions

of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. The amount of additional therapeutic agent in the presently disclosed compositions will range from about 10% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00219] The compounds of this invention or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the invention, in another aspect, includes a composition for coating an implantable device comprising a compound of the invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. In still another aspect, the invention includes an implantable device coated with a composition comprising a compound of the invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccarides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

[00220] Another aspect of the invention relates to inhibiting $Na_V1.8$ activity in a biological sample or a subject, which method comprises administering to the subject, or contacting said biological sample with a compound of formula I or a composition comprising said compound. 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.

[00221] Inhibition of $Na_V1.8$ 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 channels in biological and pathological

phenomena; and the comparative evaluation of new sodium channel inhibitors.

SCHEMES AND EXAMPLES

[00222] The following definitions describe terms and abbreviations used herein:

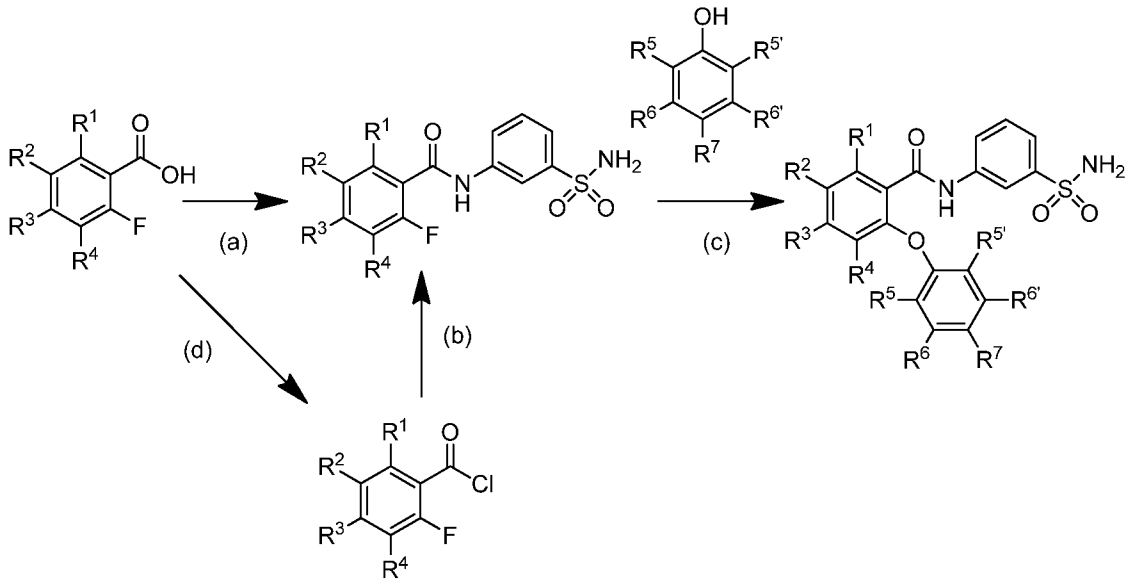
Ac	acetyl
Bu	butyl
Et	ethyl
Ph	phenyl
Me	methyl
THF	tetrahydrofuran
DCM	dichloromethane
CH_2Cl_2	dichloromethane
EtOAc	ethyl acetate
CH_3CN	acetonitrile
MeCN	acetonitrile
ACN	acetonitrile
EtOH	ethanol
Et_2O	diethyl ether
MeOH	methanol
i-PrOH	isopropyl alcohol
MTBE	methyl *tert*-butyl ether
DMF	*N,N*-dimethylformamide
DMA	*N,N*-dimethylacetamide
DMSO	dimethyl sulfoxide
HOAc	acetic acid
NMP	N-methylpyrrolidinone
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
Et_3N or NEt_3	triethylamine
DIPEA or DIEA	diisopropylethylamine
K_2CO_3	potassium carbonate
Na_2CO_3	sodium carbonate
$Na_2S_2O_3$	sodium thiosulfate
Cs_2CO_3	cesium carbonate
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
Na_2SO_4	sodium sulfate
$MgSO_4$,	magnesium sulfate
K_3PO_4	potassium phosphate
NH_4Cl	ammonium chloride
SO_2Cl_2	thionyl chloride
$KMnO_4$	potassium permanganate
DMAP	N,N-dimethylaminopyridine

HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxid hexafluorophosphate
EDCI	N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride
HOBT	1-hydroxybenzotriazole hydrate
HCl	hydrochloric acid
H_2O	water
Pd/C	palladium on carbon
NaOAc	sodium acetate
H_2SO_4	sulfuric acid
N_2	nitrogen gas
H_2	hydrogen gas
n-BuLi	*n*-butyl lithium
$Pd(OAc)_2$	palladium(II)acetate
PPh_3	triphenylphosphine
NBS	*N*-bromosuccinimide
$Pd[(Ph_3)P]_4$	tetrakis(triphenylphosphine)palladium(0)
LC/MS	liquid chromatography/mass spectra
GCMS	gas chromatography mass spectra
HPLC	high performance liquid chromatography
GC	gas chromatography
LC	liquid chromatography
IC	ion chromatography
Hr or h	hours
min	minutes
atm	atmospheres
rt or RT	room temperature
TLC	thin layer chromatography
SM	starting material
Equiv. or Eq.	equivalents
aq	aqueous
N	normal
L	liters
mL	milliliters
µL	microliters
M	molar
µM	micromolar
nM	nanomolar
N	normal
mol	moles
mmol	millimoles
g	grams
mg	milligrams
µg	micrograms
^{1}H-NMR	proton nuclear magnetic resonance
MHz	megahertz
Hz	hertz

$CDCl_3$	deutero chloroform
DMSO-d6	deutero dimethyl sulfoxide
MeOD	deutero methanol
CD_3OD	deutero methanol
K_i	dissociation constant
IC_{50}	half maximal inhibitory concentration

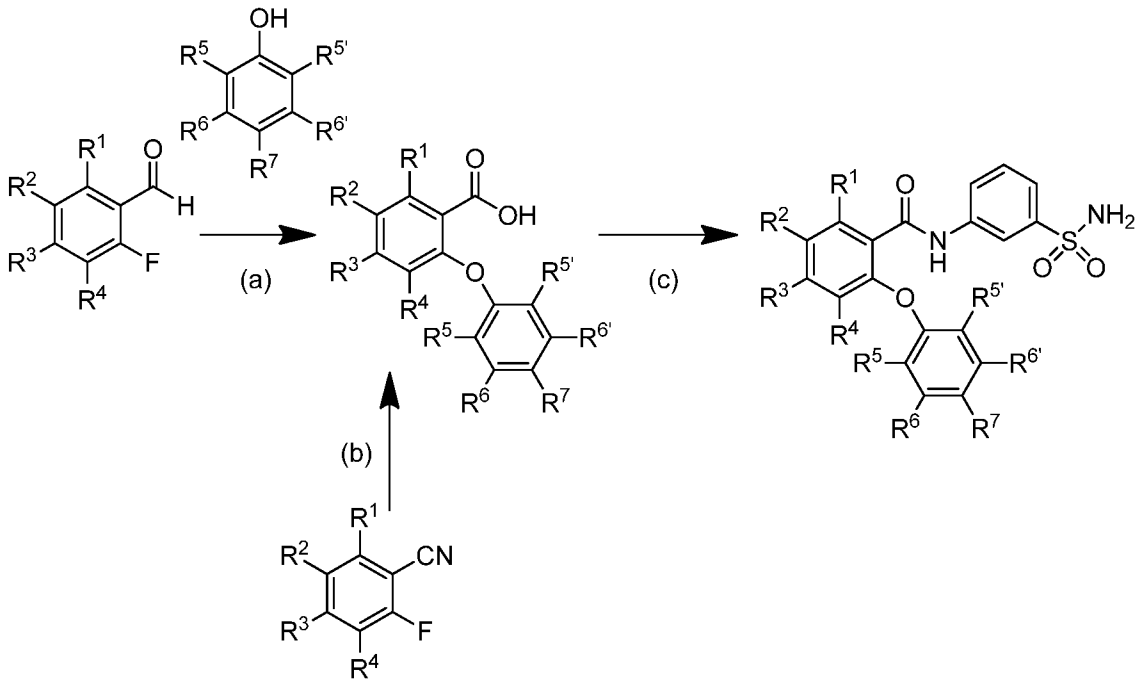
[00223] The compounds of the invention may be prepared readily using the following methods. Illustrated below in Schemes 1-3 are general methods for preparing the compounds of the present invention.

Scheme 1: General Preparation of Compounds of Formula I



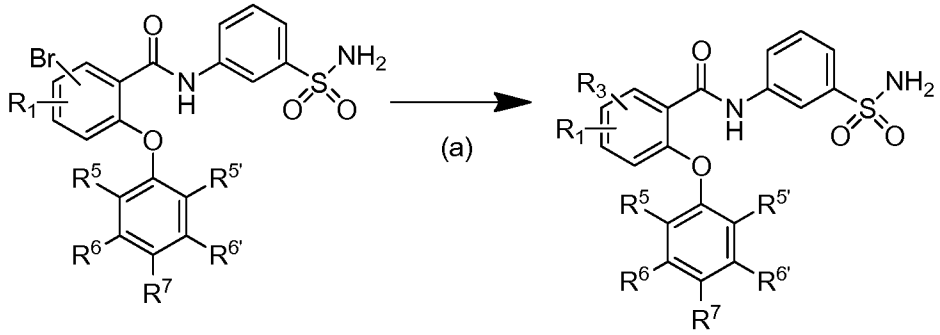
(a) 3-aminophenyl sulfonamide, coupling agent (i.e. HATU, EDCI, HOBT), base (i.e. N-methylmorpholine), solvent (i.e. DMF, dichloromethane); (b) 3-aminophenyl sulfonamide, base (i.e. pyridine, Cs_2CO_3), solvent (i.e. dichloromethane, DMF); (c) base (i.e. NaH, Cs_2CO_3, Na_2CO_3, $NaHCO_3$), solvent (DMF, NMP, dioxane), ΔT; (d) SO_2Cl_2, DMF in a solvent (i.e. dichloromethane).

Scheme 2: General Preparation of Compounds of Formula I



(a) i) base (i.e. NaH, Cs_2CO_3, Na_2CO_3, $NaHCO_3$), solvent (DMF, NMP, dioxane), ΔT; ii) oxidation conditions (i.e. $KMnO_4$ or sodium dihydrogen phosphate, 2-methyl-2-butene and sodium chlorite) in a solvent (water, tBuOH and acetonitrile); (b) i) base (i.e. NaH, Cs_2CO_3, Na_2CO_3, $NaHCO_3$), solvent (DMF, NMP, dioxane), ΔT; ii) Hydrolysis conditions (i.e. aqueous HBr); (c) 3-aminophenyl sulfonamide, coupling agent (i.e. HATU, EDCI, HOBT), base (i.e. N-methylmorpholine), solvent (i.e. DMF, dichloromethane).

Scheme 3: General Preparation of Compounds of Formula I



(a) R_3-$B(OH)_2$ (i.e. $MeB(OH)_2$, Pd catalyst (i.e. $(PPh_3)_4Pd$), solvent (i.e. dimethoxyethane), base (i.e. Na_2CO_3).

[00224] Scheme 3 above may be used to insert a variety of R^1, R^2, R^3 and R^4 groups starting with the aryl bromide. The scheme above shows the presence of, for instance, an R^1 group and an aryl bromide which is reacted with a suitable boronic acid under Suzuki

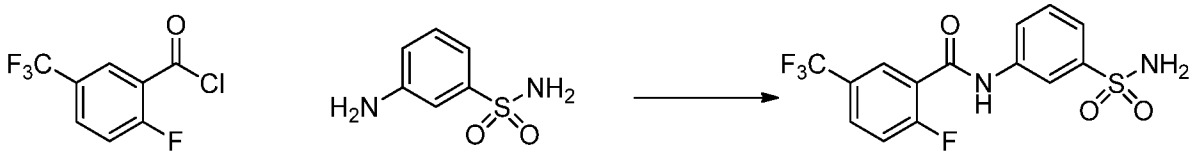
type conditions to replace the bromide group with an R^3 moiety. One of skill in the art would recognize that a variety of R^1 through R^4 groups could be inserted from the starting aryl bromide through this procedure.

EXAMPLES

[00225] **General methods.** ^{1}H NMR (400 MHz) spectra were obtained as solutions in an appropriate deuterated solvent such as dimethyl sulfoxide-d_6 (DMSO). Mass spectra (MS) were obtained using an Applied Biosystems API EX LC/MS system. Compound purity and retention times were determined by reverse phase HPLC using a Kinetix C18 column (50 × 2.1 mm, 1.7 μm particle) from Phenomenex (pn: 00B-4475-AN)), and a dual gradient run from 1-99% mobile phase B over 3 minutes. Mobile phase A = H_20 (0.05 % CF_3CO_2H). Mobile phase B = CH_3CN (0.05 % CF_3CO_2H). Flow rate = 2 mL/min, injection volume = 3 μL, and column temperature = 50 °C. Silica gel chromatography was performed using silica gel-60 with a particle size of 230-400 mesh. Pyridine, dichloromethane, tetrahydrofuran, dimethylformamide, acetonitrile, methanol, 1,4-dioxane and other commonly used solvetns were from, for example, Baker or Aldrich and in some cases the reagents were Aldrich Sure-Seal bottles kept under dry nitrogen. All reactions were stirred magnetically unless otherwise noted.

EXAMPLE 1

Preparation of 2-fluoro-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide

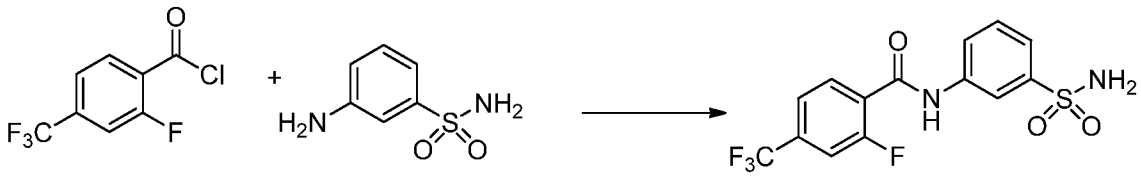


[00226] To a solution of 3-aminobenzenesulfonamide (18.77 g, 109.0 mmol) and pyridine (88.16 mL, 1.090 mol) in dichloromethane (247.0 mL) at 0 °C was added dropwise 2-fluoro-5-(trifluoromethyl)benzoyl chloride (24.7 g, 109.0 mmol). The mixture was allowed to warm to room temperature and was stirred for 18 hours. The reaction mixture was diluted with dichloromethane and water. The layers were separated and the organic layer washed with aqueous 1N HCl (2x). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was triturated with dichloromethane

and filtered. The white solid was washed with diethyl ether and was collected via vacuum filtration to give 2-fluoro-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide (23.83 g, 60%) as a white solid. ESI-MS *m/z* calc. 362.03, found 363.3 $(M+1)^+$; Retention time: 1.37 minutes (3 min run). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 8.30 (s, 1H), 8.15 - 8.07 (m, 1H), 8.06 - 7.97 (m, 1H), 7.89 - 7.83 (m, 1H), 7.64 (t, J = 9.2 Hz, 1H), 7.62 - 7.54 (m, 2H), 7.42 (s, 2H) ppm.

EXAMPLE 2

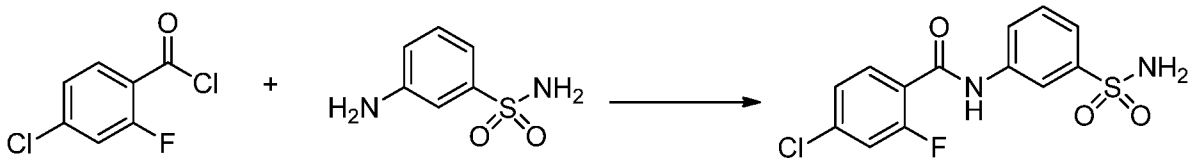
Preparation of 2-fluoro-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide



[00227] To a solution of 3-aminobenzenesulfonamide (3.8 g, 22.07 mmol) and 2-fluoro-4-(trifluoromethyl)benzoyl chloride (5 g, 22.07 mmol) in dichloromethane (90 mL) was added pyridine (10.7 mL, 132.4 mmol) and the mixture was stirred at room temperature for 15 hours. Water (50 mL) was added to the reaction and the product crashed out. The solid was isolated by filtration, washed with water (2 x 75 mL), and dried under vacuum to yield 2-fluoro-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide (4.43 g) as a cream solid. The solvent was evaporated under reduced pressure. Water was added and the mixture was set aside. After a few minutes, solid precipitated. The solid was isolated by filtration, washed with water (2 x 30 mL), and dried under vacuum to yield a second crop of the desired product (2.7 g). The two crops were combined to yield 2-fluoro-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide (7.13g, 88%) as a solid. ESI-MS *m/z* calc. 362.03, found 363.3 $(M+1)^+$; Retention time: 1.63 minutes (3 minutes run). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 8.35 - 8.27 (m, 1H), 7.99 - 7.88 (m, 2H), 7.88 - 7.80 (m, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.65 - 7.51 (m, 2H), 7.43 (s, 2H) ppm.

EXAMPLE 3

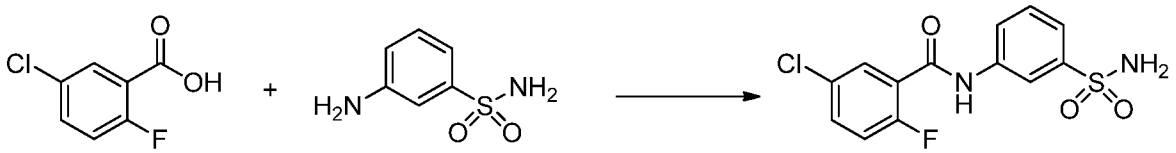
Preparation of 4-chloro-2-fluoro-N-(3-sulfamoylphenyl)benzamide



[00228] Pyridine (939.0 μL, 11.61 mmol) was added slowly to a solution of 4-chloro-2-fluoro-benzoyl chloride (1.1 g, 5.81 mmol) and 3-aminobenzenesulfonamide (1 g, 5.81 mmol) in dichloromethane (5 mL). The reaction was stirred at room temperature for 1 hour. The reaction mixture was filtered and the precipitate was washed with dichloromethane and water to give 4-chloro-2-fluoro-N-(3-sulfamoylphenyl)benzamide (1.8 g, 92.2%) as a white solid. ESI-MS *m/z* calc. 328.01, found 329.1 $(M+1)^+$; Retention time: 1.47 minutes (3 minutes run). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.78 (s, 1H), 8.31 (s, 1H), 7.84 (d, J = 6.8 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.66 (dd, J = 10.0, 1.9 Hz, 1H), 7.57 (m, 2H), 7.46 (dd, J = 8.3, 1.9 Hz, 1H), 7.41 (s, 2H) ppm.

EXAMPLE 4

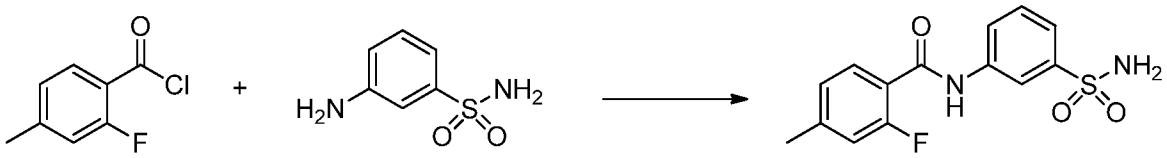
Preparation of 5-chloro-2-fluoro-N-(3-sulfamoylphenyl)benzamide



[00229] A mixture of 5-chloro-2-fluoro-benzoic acid (349.1 mg, 2.0 mmol), 3-aminobenzenesulfonamide (413.3 mg, 2.4 mmol), HATU (608.4 mg, 1.6 mmol), and N-methylmorpholine (439.8 μL, 4.0 mmol) in DMF (4 mL) was stirred at 40 °C for 1 hour. The reaction mixture was poured into water, the pH was adjusted to 4, and the mixture was extracted with ethyl acetate (3x). The organics were combined, washed with water, brine, dried over Na_2SO_4, filtered and evaporated to dryness to give 5-chloro-2-fluoro-N-(3-sulfamoylphenyl)benzamide (0.36 g, 55%) as an pale yellow solid. ESI-MS *m/z* calc. 328.01, found 329.1 $(M+1)^+$; Retention time: 1.41 minutes (3 minutes run).

EXAMPLE 5

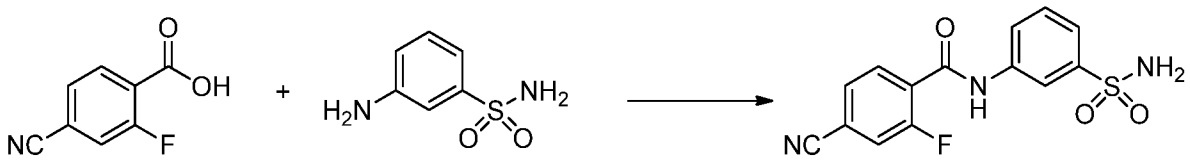
Preparation of 2-fluoro-4-methyl-N-(3-sulfamoylphenyl)benzamide



[00230] Pyridine (1.0 mL, 12.98 mmol) was added dropwise to a mixture of 2-fluoro-4-methyl-benzoyl chloride (2.24 g, 12.98 mmol), 3-aminobenzenesulfonamide (2.235 g, 12.98 mmol) and dichloromethane (40.32 mL) at room temperature. The mixture was allowed to stir at room temperature for 2.5 hours before water (150 mL) was added. The mixture was filtered and the solid was collected by vacuum filtration. The solid was slurried with diethyl ether (30 mL) and filtered (twice). The solid was placed in a vacuum oven at 40 °C overnight to give 2-fluoro-4-methyl-N-(3-sulfamoylphenyl)benzamide (1.81 g, 45%) as an off-white solid. ESI-MS *m/z* calc. 308.06, found 309.5 $(M+1)^+$; Retention time: 1.42 minutes (3 minutes run). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 8.32 (s, 1H), 7.89 - 7.80 (m, 1H), 7.62 - 7.51 (m, 3H), 7.39 (s, 2H), 7.24 - 7.11 (m, 2H), 2.39 (s, 3H) ppm.

EXAMPLE 6

Preparation of 4-cyano-2-fluoro-N-(3-sulfamoylphenyl)benzamide

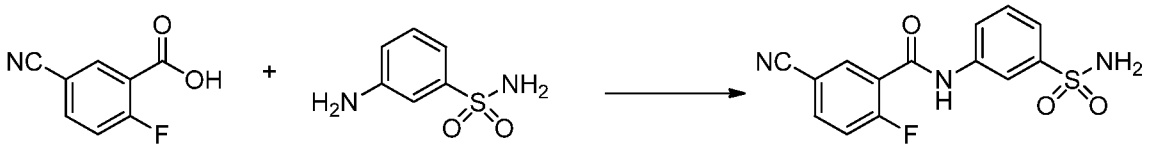


[00231] A solution of 4-cyano-2-fluoro-benzoic acid (495.4 mg, 3.0 mmol), 3-aminobenzenesulfonamide (516.6 mg, 3.0 mmol), EDCI (575.1 mg, 3.0 mmol), HOBT (405.4 mg, 3.0 mmol) and N-methylmorpholine (659.7 µL, 6.0 mmol) in DMF (4 mL) was stirred at 25 °C for 16 hours. The reaction mixture was poured into 1N HCl and extracted with ethyl acetate (3x). The organics were combined and washed with 1N HCl (3x), water, brine, dried over Na_2SO_4, filtered through a short plug of silica and evaporated to dryness to yield 4-cyano-2-fluoro-N-(3-sulfamoylphenyl)benzamide (860 mg, 90%) as a white solid that was

used in the next steps without further purification. ESI-MS *m/z* calc. 319.04, found 320.1 $(M+1)^+$; Retention time: 1.04 minutes (3 minutes run).

EXAMPLE 7

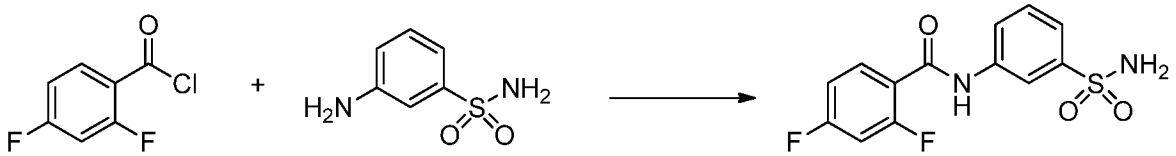
Preparation of 5-cyano-2-fluoro-N-(3-sulfamoylphenyl)benzamide



[00232] A solution of 5-cyano-2-fluoro-benzoic acid (165.1 mg, 1.0 mmol), 3-aminobenzenesulfonamide (206.6 mg, 1.20 mmol), HATU (342.2 mg, 0.90 mmol) and N-methylmorpholine (219.9 µL, 2.0 mmol) in DMF (2 mL) was stirred at 25 °C for 4 hours. The reaction mixture was poured into water and extracted with ethyl acetate (3x). The organics were combined, washed with water, acidified to pH ~ 4 with 1N HCl and extracted with ethyl acetate (3x). The organics were combined, washed with water, brine, dried with Na_2SO_4, filtered and evaporated to dryness to give 5-cyano-2-fluoro-N-(3-sulfamoylphenyl)benzamide (150 mg, 47%) that was used in the next steps without further purification. ESI-MS *m/z* calc. 319.04, found 320.1 $(M+1)^+$; Retention time: 0.97 minutes (3 minutes run).

EXAMPLE 8

Preparation of 2,4-difluoro-N-(3-sulfamoylphenyl)benzamide

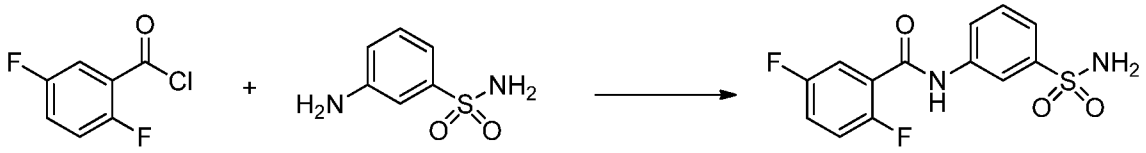


[00233] To a mixture of 2,4-difluorobenzoyl chloride (2.0 g, 11.33 mmol), 3-aminobenzenesulfonamide (1.95 g, 11.33 mmol) and dichloromethane (36.0 mL) was added pyridine (3.7 mL, 45.32 mmol) at 25 °C . The mixture was allowed to stir at 25 °C for 18h before it was washed with 1N HCl and water. The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was subjected to column chromatography (0-100% ethyl acetate/hexanes) to give 2,4-difluoro-N-(3-sulfamoylphenyl)benzamide (2.0 g, 57%) . ESI-MS *m/z* calc. 312.04, found 313.1 $(M+1)^+$; Retention time: 1.31 minutes (3

minutes run). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 8.31 (s, 1H), 7.89 - 7.74 (m, 2H), 7.62 - 7.52 (m, 2H), 7.51 - 7.42 (m, 1H), 7.41 (s, 2H), 7.26 (td, J = 8.4, 2.2 Hz, 1H) ppm.

EXAMPLE 9

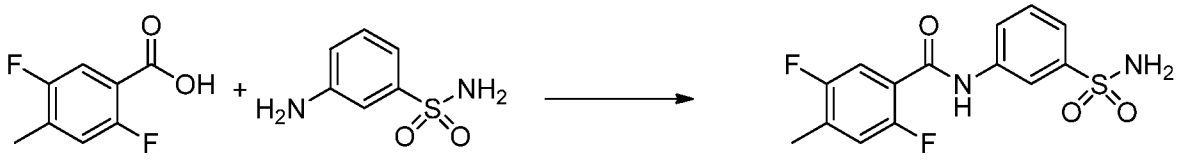
Preparation of 2,5-difluoro-N-(3-sulfamoylphenyl)benzamide



[00234] To a solution of 3-aminobenzenesulfonamide (1.0 g, 5.81 mmol) and pyridine (4.7 mL, 58.07 mmol) in dichloromethane (10.3 mL) at 0 °C was added dropwise 2,5-difluorobenzoyl chloride (719.3 μL, 5.81 mmol). The mixture was allowed to warm to 25 °C and was stirred for 72 hours. The reaction mixture was diluted with ethyl acetate and water. The layers were separated and the organic layer washed with brine (2x). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to give a clear oil that crystallized upon standing. The solid was re-dissolved in ethyl acetate and washed with 1N HCl (3x). The organic layer was dried with $MgSO_4$, filtered and evaporated to yield 2,5-difluoro-N-(3-sulfamoylphenyl)benzamide (1.17 g, 64%) as a white solid. ESI-MS *m/z* calc. 312.04, found 313.3 $(M+1)^+$; Retention time: 1.31 minutes (3 minutes run). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H), 8.31 (s, 1H), 7.84 (d, J = 9.1 Hz, 1H), 7.59 - 7.54 (m, 3H), 7.50 - 7.39 (m, 4H) ppm.

EXAMPLE 10

Preparation of 2,5-difluoro-4-methyl-N-(3-sulfamoylphenyl)benzamide

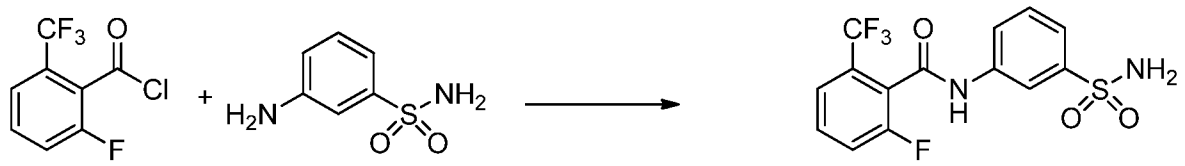


[00235] A solution of 3-aminobenzenesulfonamide (413.3 mg, 2.40 mmol), 2,5-difluoro-4-methyl-benzoic acid (344.3 mg, 2.0 mmol), HATU (684.4 mg, 1.80 mmol) and N-methylmorpholine (439.8 μL, 4.0 mmol) in DMF (2 mL) was stirred at 40 °C for 2 hours. The reaction was poured into 1N HCl and extracted with ethyl acetate (3x). The organics were

combined, washed with water, brine, dried with Na_2SO_4 and evaporated to dryness to give 2,5-difluoro-4-methyl-N-(3-sulfamoylphenyl)benzamide (610 mg, 94%) as a solid that was used in the next step without further purification. ESI-MS *m/z* calc. 326.05, found 327.3 $(M+1)^+$; Retention time: 1.25 minutes (3 minutes run).

EXAMPLE 11

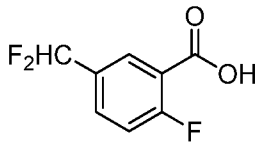
Preparation of 2-fluoro-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide



[00236] To a solution of 3-aminobenzenesulfonamide (760.1 mg, 4.41 mmol) in dichloromethane (10 mL) was added 2-fluoro-6-(trifluoromethyl)benzoyl chloride (1 g, 4.41 mmol), 3-aminobenzenesulfonamide (760.1 mg, 4.41 mmol) and pyridine (1.1 mL, 13.24 mmol) and the mixture was stirred at 25 °C for 12 hours. The reaction was diluted with dichloromethane and water. The 2 layers were separated and the organic layer washed with water and 1N HCl. The organics were combined and evaporated to yield 2-fluoro-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide (600 mg, 37%) a s a light pink solid. ESI-MS *m/z* calc. 362.03, found 363.3 $(M+1)^+$; Retention time: 1.39 minutes (3 minutes run). ^1H NMR (400 MHz, CD_3CN) δ 9.18 (s, 1H), 8.31 (t, J = 1.9 Hz, 1H), 7.83 - 7.43 (m, 6H), 5.75 (s, 2H) ppm.

EXAMPLE 12

Preparation of 5-(difluoromethyl)-2-fluorobenzoic acid



[00237] 2-Fluoro-5-methyl-benzoic acid (2 g, 12.98 mmol), NBS (6.0 g, 33.75 mmol) and benzoyl peroxide (157.2 mg, 0.65 mmol) in CCl_4 (30 mL) was heated at reflux for 48 hours. The solids were filtered off and washed with dichloromethane. The solvent was evaporated and the residue was taken up in ethanol (30 mL) and heated to 50 °C. A solution of silver nitrate (2.20 g, 12.98 mmol) in 5 ml water was added drop wise. The mixture was

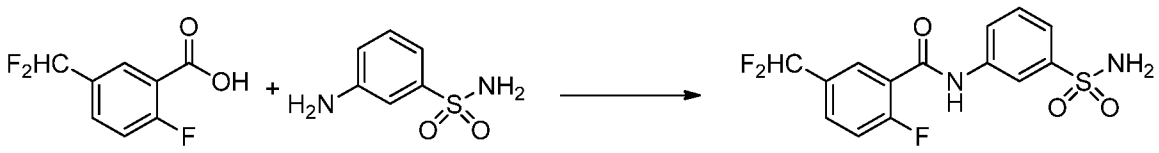
stirred for 45 minutes, cooled to 25 °C, then poured into 1N HCl. The solids were filtered off and washed with EtOH. The EtOH was removed and the aqueous layer was extracted with ethyl acetate (3x). The organics were combined, washed with brine, dried over Na_2SO_4 and evaporated to dryness. Purification by column chromatography using a gradient of ethyl acetate in hexanes (0 - 50%) gave 2-fluoro-5-formyl-benzoic acid (0.33 g, 15%) as a light yellow solid. ESI-MS m/z calc. 168.02, found 169.1 $(M+1)^+$; Retention time: 0.49 minutes (3 minutes run). ^1H NMR (400 MHz, DMSO-d_6) δ 13.64 (s, 1H), 10.03 (s, 1H), 8.43 (dd, J = 7.2, 2.2 Hz, 1H), 8.17 (ddd, J = 8.4, 4.7, 2.2 Hz, 1H), 7.56 (dd, J = 10.6, 8.6 Hz, 1H) ppm.

[00238] Deoxofluor (566.8 µL, 3.07 mmol) was added to methyl 2-fluoro-5-formyl-benzoate (280 mg, 1.54 mmol) followed by 2 drops of ethanol and the reaction mixture was stirred at 25 °C for 4 hours. More deoxofluor (100 µL, 0.54 mmol) was added and the reaction mixture was stirred for an additional hour. The mixture was carefully quenched with saturated aqueous solution of sodium bicarbonate and then extracted with ethyl acetate (3x). The organics were combined, washed with water, brine, dried over Na_2SO_4, filtered and evaporated to dryness. Purification by column chromatography using a gradient of ethyl acetate in hexanes (0 - 20%) gave methyl 5-(difluoromethyl)-2-fluoro-benzoate (230 mg, 73%) as a clear oil. ESI-MS *m/z* calc. 204.04, found 204.9 $(M+1)^+$; Retention time: 1.31 minutes (3 minutes run). ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 - 8.05 (m, 1H), 7.81 - 7.58 (m, 1H), 7.29 - 7.19 (m, 1H), 6.66 (t, J = 56.1 Hz, 1H), 3.96 (s, 3H) ppm.

[00239] To a solution of methyl 5-(difluoromethyl)-2-fluoro-benzoate (230 mg, 1.127 mmol) in THF (4 mL) was added a solution of LiOH (269.9 mg, 11.27 mmol) in water (1 mL) and the reaction mixture was stirred at 25 °C for 4 hours. The reaction was brought to pH 4 with 4N HCl and then extracted with ethyl acetate (3x). The organics were combined, washed with water, brine, dried over Na_2SO_4, filtered and evaporated to dryness to give 5-(difluoromethyl)-2-fluoro-benzoic acid (187 mg, 87%) as a white solid. ESI-MS *m/z* calc. 190.02, found 191.3 $(M+1)^+$; Retention time: 1.0 minutes (3 minutes run).

EXAMPLE 13

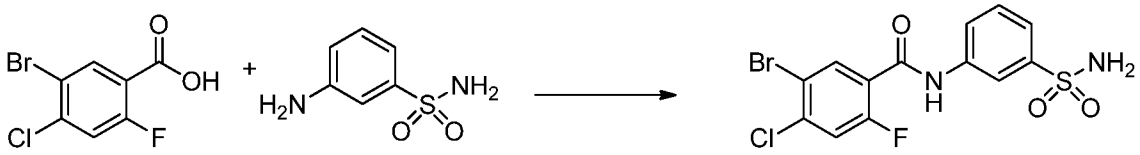
Preparation of 5-(difluoromethyl)-2-fluoro-N-(3-sulfamoylphenyl)benzamide



[00240] To a solution of 5-(difluoromethyl)-2-fluoro-benzoic acid (95.1 mg, 0.50 mmol), 3-aminobenzenesulfonamide (94.7 mg, 0.55 mmol), and N-methylmorpholine (109.9 μL, 1.0 mmol) in DMF (1 mL) was added HATU (209 mg, 0.55 mmol) and the reaction mixture was stirred at 25 °C for 1 hour. The reaction was poured into 1N HCl and extracted with ethyl acetate (3x). The organics were combined, washed with water (2x), brine, dried with Na_2SO_4, filtered and evaporated to dryness. Purification by silica gel column chromatography using a 20 - 80% gradient of ethyl acetate in hexanes gave 5-(difluoromethyl)-2-fluoro-N-(3-sulfamoylphenyl)benzamide (202 mg, >100%) that was used in the next step without further purification. ESI-MS *m/z* calc. 344.04, found 345.3 $(M+1)^+$; Retention time: 1.19 minutes (3 minutes run).

EXAMPLE 14

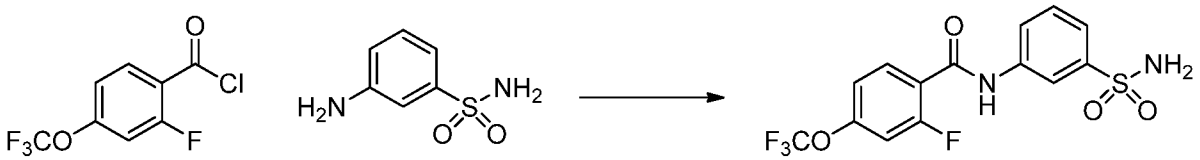
Preparation of 5-bromo-4-chloro-2-fluoro-N-(3-sulfamoylphenyl)benzamide



[00241] To 5-bromo-4-chloro-2-fluoro-benzoic acid (5.0 g, 19.73 mmol), 3-aminobenzenesulfonamide (5.1 g, 29.60 mmol), 1-hydroxybenzotriazole (2.93 g, 21.70 mmol), 3-(ethyliminomethyleneamino)-N,N-dimethyl-propan-1-amine hydrochloride (4.2 g, 21.70 mmol), and N,N-dimethylformamide (80 mL), triethyl amine (5.5 mL, 39.46 mmol) was added and stirred at room temperature for 18 hours. The solvent was evaporated. The reaction was washed with a 1M solution of hydrochloric acid (3 x 50 mL), a saturated aqueous solution of sodium bicarbonate (3 x 50 mL), and a saturated aqueous solution of sodium chloride (3 x 50 mL). The organic layer was dried over sodium sulfate, filtered, and evaporated to dryness. The crude product was dissolved in dichloromethane and the precipitate was isolated by filtration to yield 5-bromo-4-chloro-2-fluoro-N-(3-sulfamoylphenyl)benzamide (4.0 g, 35%) as a grey solid. The product was used in the next step without further purification. ESI-MS m/z calc. 405.92, found 407.0 (M+1)+; Retention time: 1.7 minutes (3 minutes run). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.32 - 8.24 (m, 1H), 8.13 (d, J = 7.0 Hz, 1H), 7.90 (d, J = 9.7 Hz, 1H), 7.86 - 7.81 (m, 1H), 7.61 - 7.53 (m, 2H), 7.42 (s, 2H) ppm.

EXAMPLE 15

Preparation of 2-fluoro-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide

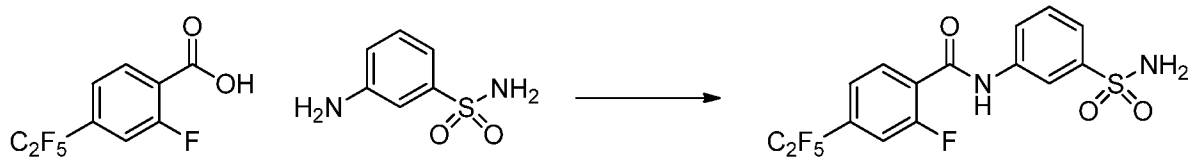


[00242] To 2-fluoro-4-(trifluoromethoxy)benzoic acid (5 g, 22.31 mmol) in thionyl chloride (2.43 mL, 33.46 mmol) was added N,N-dimethylformamide (491.6 µL, 6.38 mmol). The reaction mixture was stirred at room temperature for 17 hours. Excess thionyl chloride and N,N-dimethyl formamide were removed *in vacuo* to yield 2-fluoro-4-(trifluoromethoxy)benzoyl chloride that was used in the next step without further purification.

[00243] To 3-aminobenzenesulfonamide (4.79 g, 27.83 mmol) was added potassium carbonate (3.85 g, 27.82 mmol), methyl *tert*-butyl ether (27.0 mL) and water (27.0 mL). The reaction was cooled to 0 °C. To the vigorously stirred reaction was added 2-fluoro-4-(trifluoromethoxy)benzoyl chloride (5.4 g, 22.26 mmol) in dichloromethane (13.5 mL). The reaction was stirred at room temperature for 30 hours. The reaction was a slurry. The product was isolated by filtration using ether. The product was loaded onto celite and purified by silica gel chromatography utilizing a gradient of 0-50% ethyl acetate in dichloromethane to yield 3 g (35%) of 2-fluoro-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.83 (s, 1H), 8.38 - 8.25 (m, 1H), 7.90 - 7.78 (m, 2H), 7.66 - 7.52 (m, 3H), 7.47 - 7.36 (m, 3H) ppm. ESI-MS m/z calc. 378.03, found 379.4 (M+1)+; Retention time: 1.56 minutes (3 minutes run).

EXAMPLE 16

Preparation of 2-fluoro-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide



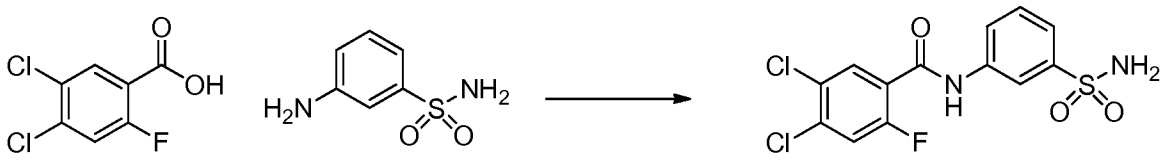
[00244] To a stirred solution of 4-bromo-2-fluoro-benzoic acid (3.0 g, 13.70 mmol) and copper (8.70 g, 137.0 mmol) in DMSO (56.3 mL) in a bomb, 1,1,1,2,2-pentafluoro-2-iodo-ethane (23.6 g, 95.90 mmol) was bubbled through. The vessel was sealed and heated at 120 °C for 72 hours. The reaction mixture was diluted with water and filtered through a plug of silica and then extracted with ethyl acetate (4x). The organics were

combined, washed with brine, dried (Na_2SO_4) and evaporated to dryness. Purification by column chromatography using a gradient of 0-40% ethyl acetate in hexanes gave 2-fluoro-4-(1,1,2,2,2-pentafluoroethyl)benzoic acid (1.81 g, 51%) as white solid. ESI-MS m/z calc. 258.01, found 259.3 (M+1)+; Retention time: 1.45 minutes.

[00245] A solution of 2-fluoro-4-(1,1,2,2,2-pentafluoroethyl)benzoic acid (516.2 mg, 2.0 mmol), 3-aminobenzenesulfonamide (378.9 mg, 2.20 mmol), HATU (836.5 mg, 2.20 mmol) and N-methylmorpholine (439.8 µL, 4.0 mmol) in DMF (6 mL) was stirred at room temperature for 16 hours. The reaction mixture was poured into water, the pH adjusted to 4 with 1N HCl and extracted with ethyl acetate (3x). The organics were combined, washed with water, brine, dried over Na_2SO_4 and evaporated to dryness. Purification by column chromatography using a gradient of 0 - 50% ethyl acetate in hexanes gave 2-fluoro-4-(1,1,2,2,2-pentafluoroethyl)-N-(3-sulfamoylphenyl)benzamide (710 mg, 86%) as a white solid. ESI-MS m/z calc. 412.03165, found 413.3 (M+1)+; Retention time: 1.5 minutes.

EXAMPLE 17

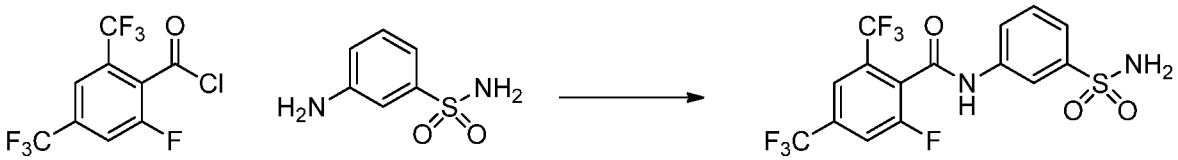
Preparation of 4,5-dichloro-2-fluoro-N-(3- sulfamoylphenyl)benzamide



[00246] A solution of 3-aminobenzenesulfonamide (271.9 mg, 1.58 mmol), 4,5-dichloro-2-fluoro-benzoic acid (300 mg, 1.43 mmol), and HATU (654.8 mg, 1.72 mmol) in DMF (3.12 mL) was treated with N-methylmorpholine (315.5 µL, 2.87 mmol) and stirred at 40 °C for 16 hours. The reaction was diluted with ethyl acetate and water and the organic layer separated. The organic layer was washed with 1 N HCl, water (3 x 50 mL), and brine, then dried over Na_2SO_4, filtered, and concentrated. The residue was slurried in dichloromethane to form a white precipitate. The precipitate was filtered and washed with dichloromethane to provide 4,5-dichloro-2-fluoro-N-(3-sulfamoylphenyl)benzamide (422 mg, 81%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.85 (s, 1H), 8.32 - 8.25 (m, 1H), 8.03 (d, J = 6.7 Hz, 1H), 7.93 (d, J = 9.5 Hz, 1H), 7.83 (dt, J = 6.8, 2.2 Hz, 1H), 7.64 - 7.52 (m, 2H), 7.42 (s, 2H) ppm. ESI-MS m/z calc. 361.96948, found 364.7 (M+1)+; Retention time: 1.4 minutes (3 minutes run).

EXAMPLE 18

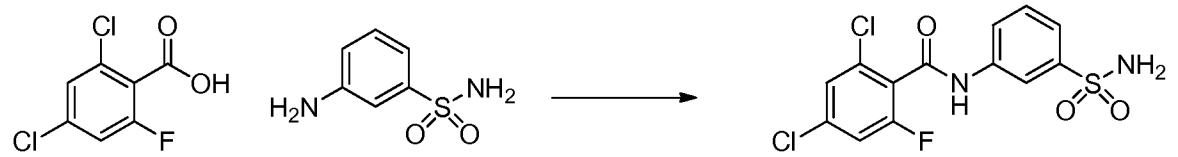
Preparation of 2-fluoro-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide



[00247] To 3-aminobenzenesulfonamide (300.8 mg, 1.75 mmol) in methyl-*tert*-butylether (2.8 mL) was added K_2CO_3 (689.9 mg, 5.0 mmol) in water (2.8 mL). The reaction was stirred at room temperature and 2-fluoro-4,6-bis(trifluoromethyl)benzoyl chloride (490 mg, 1.66 mmol) in methyl-tert-butylether (2.8 mL) was added dropwise. The reaction was stirred at room temperature for 40 minutes. Ethyl acetate (50ml) was added and the organic layer was separated, washed with brine, and concentrated to yield 2-fluoro-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide (162 mg, 23%) as a pink solid that was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.27 (s, 1H), 8.49 - 8.35 (m, 1H), 8.31 - 8.08 (m, 2H), 7.74 (dt, J = 7.5, 1.9 Hz, 1H), 7.69 - 7.54 (m, 2H), 7.46 (s, 2H) ppm.

EXAMPLE 19

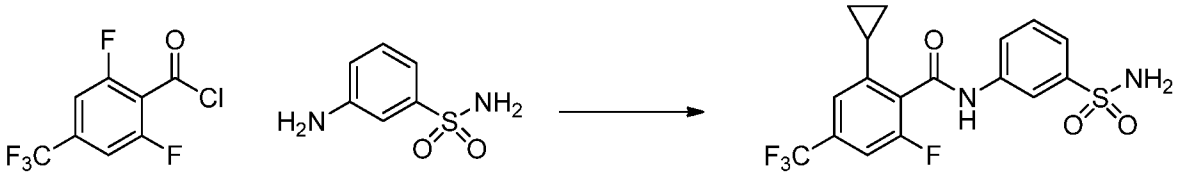
Preparation of 2,4-dichloro-6-fluoro-N-(3-sulfamoylphenyl)benzamide



[00248] To a solution of 2,4-dichloro-6-fluoro-benzoic acid (400 mg, 1.91 mmol), 3-aminobenzenesulfonamide (329.6 mg, 1.91 mmol), and HATU (727.8 mg, 1.91 mmol) in DMF (4 mL) was added N-methylmorpholine (210.4 μL, 1.91 mmol) and thereaction mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into 1N HCl and extracted with ethyl acetate (3x). The organics were combined, washed with 1N HCl, water, brine, dried over Na_2SO_4, filtered and evaporated to dryness. Purification by column chromatography using a gradient of ethyl acetate in hexanes 1 - 50% gave 2,4-dichloro-6-fluoro-N-(3-sulfamoylphenyl)benzamide (420 mg, 60%) as a white solid.

EXAMPLE 20

Preparation of 2-cyclopropyl-6-fluoro-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide



[00249] To a mixture of 2,6-difluoro-4-(trifluoromethyl)benzoic acid (500 mg, 2.21 mmol) in THF (4.0 mL) was slowly added bromo(cyclopropyl)magnesium (12.0 mL of 0.5 M, 6.00 mmol). The reaction was stirred at room temperature for one hour then at 55 °C for one hour. To the reaction was added additional bromo(cyclopropyl)magnesium (8.84 mL of 0.5 M, 4.42 mmol) and the reaction was stirred at 55°C for 12 additional hours. The reaction mixture was carefully poured into 50ml of saturated NH_4Cl and was extracted with ethyl acetate. The organic layer was washed with water. The combined water layers were acidified to pH=3 using 1N HCl and were extracted with ethyl acetate (2 X 50ml), dried over sodium sulfate, filtered and concentrated to provide 2-cyclopropyl-6-fluoro-4-(trifluoromethyl)benzoic acid (345 mg, 63%) that was used in the next step withourt further purification. ESI-MS m/z calc. 248.05, found 249.15 (M+1)+; Retention time: 0.59 minutes (1 minute run). ^{1}H NMR (400 MHz, DMSO-d6) δ 7.91 - 7.43 (m, 1H), 7.12 (s, 1H), 2.04 (tt, J = 8.4, 5.2 Hz, 1H), 1.09 - 0.98 (m, 2H), 0.89 - 0.80 (m, 2H) ppm.

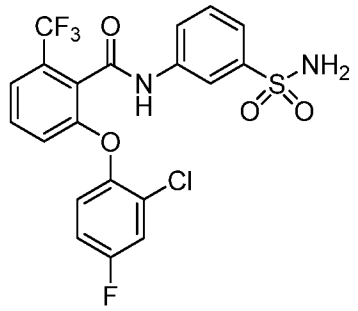
[00250] 2-Cyclopropyl-6-fluoro-4-(trifluoromethyl)benzoic acid (345 mg, 1.39 mmol), toluene (3.4 mL) and pyridine (5.6 µL, 0.069 mmol) were added to a reaction vessel and the mixture was heated to 60°C under an inert atmosphere. To the reaction mixture was added $SOCl_2$ (202.8 µL, 2.780 mmol)and the mixture was stirred for 90 minutes. Additional $SOCl_2$ (900 µl, 12.34 mmol) was added and the mixture was concentrated *in vacuo*. Toluene was added and the mixture concentrated again to give a product that was used in the next step without further purification.

[00251] To 3-aminobenzenesulfonamide (271.4 mg, 1.576 mmol) in methyl-*t*-butyl ether (1.99 mL) and DMF (1 mL) was added K_2CO_3 (544.4 mg, 3.94 mmol) in water (1.99 mL). The reaction was stirred at room temperature and 2-cyclopropyl-6-fluoro-4-(trifluoromethyl)benzoyl chloride (350 mg, 1.31 mmol) in methyl-*t*-butyl ether (1.99 mL) was added dropwise. The reaction was stirred at room temperature overnight after which 50ml of

ethyl acetate were added. The 2 layers were separated and the organic layer was washed with brine, dried with $MgSO_4$, filtered and concentrated to yield 2-cyclopropyl-6-fluoro-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide (220 mg, 42%) as a pink solid that was used in the next step without further purification. ESI-MS m/z calc. 402.07, found 403.1 (M+1)+; Retention time: 0.59 minutes (1 minute run).

EXAMPLE 21

Preparation of 2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide (**33**)



[00252] To a solution of 2-chloro-4-fluoro-phenol (21 g, 143.1 mmol) and 2-fluoro-6-(trifluoromethyl)benzaldehyde (25 g, 130.1 mmol) in DMF (125.0 mL) was added Cs_2CO_3 (46.6 g, 143.1 mmol) and the reaction mixture was stirred at 100 °C for 1 hour. The mixture was poured into water (500 ml) and extracted with ethyl acetate (3 x 150 ml). The organics were combined, washed with water, brine (2x), dried over Na_2SO_4, filtered and evaporated to give a red oil that solidified after standing over night. The material was then triturated with hot hexanes and cooled to 25 °C. The slurry was filtered and washed with cold hexanes to give 2-(2-chloro-4-fluoro-phenoxy)-6-(trifluoromethyl)benzaldehyde (32.7 g, 79%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 7.84 - 7.70 (m, 2H), 7.66 (d, J = 7.9 Hz, 1H), 7.47 (dd, J = 9.0, 5.3 Hz, 1H), 7.42 - 7.32 (m, 1H), 7.12 (d, J = 8.3 Hz, 1H) ppm.

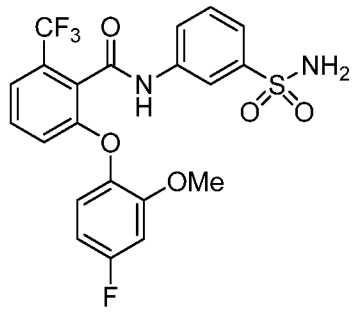
[00253] To a solution of 2-(2-chloro-4-fluoro-phenoxy)-6-(trifluoromethyl)benzaldehyde (31 g, 97.3 mmol) in *t*BuOH (155.0 mL), water (100.8 mL), CH_3CN (155.0 mL) and 2-methyl-2-butene (51.45 mL, 486.4 mmol) was added sodium dihydrogen phosphate (18.3 mL, 291.9 mmol) and the mixture was cooled to 0 °C. Sodium chlorite (26.40 g, 291.9 mmol) was added in one portion and the mixture was stirred at 25 °C for 1 hour. The pH of the mixture was adjusted to 2-3 with 1N HCl and the layers separated.

The aqueous was extracted with ethyl acetate (3 X). All organic layers were combined, and in the separatory funnel, solid sodium sulfite (~5 g) was added followed by brine (50 ml) and 1N NaOH (10 ml) and the mixture was shaken until the yellow color was gone. The layers were separated and the organic was washed with brine, dried with Na_2SO_4, filtered through a short plug of silica gel and evaporated to dryness to give 2-(2-chloro-4-fluoro-phenoxy)-6-(trifluoromethyl)benzoic acid (40 g, 98%) as an oil that was used in the next step without further purification. ESI-MS m/z calc. 334.00, found 335.1 $(M+1)^+$; Retention time: 1.78 minutes (3 minutes run).

[00254] To a stirred solution of 2-(2-chloro-4-fluoro-phenoxy)-6-(trifluoromethyl)benzoic acid (20 g, 47.81 mmol) in NMP (110 mL) was added HATU (16.36 g, 43.03 mmol) followed by 3-aminobenzenesulfonamide (9.88 g, 57.37 mmol) and N-methylmorpholine (10.51 mL, 95.60 mmol) and the mixture was heated to 80 °C and stirred at this temperature for 4 hours. The reaction was recharged with 3-aminobenzenesulfonamide (4.12 g, 23.91 mmol) was stirred at 80 °C for 13 hours. The mixture was poured into 1N HCl (400 ml) and extracted with ethyl acetate (3 x 200 ml). The organics were combined, washed with 1N HCl (2 x 400 ml), water (2 x 400 ml), brine and then dried with Na_2SO_4, filtered and evaporated to dryness to yield a crude mixture that was purified by silica gel column chromatography using a gradient of ethyl acetate and hexanes (0 - 50%) to give the desired product as a white foam. After drying under vacuum, 2-(2-chloro-4-fluoro-phenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide (**33**) (14 g, 60%) was obtained as a white solid. ESI-MS m/z calc. 488.02, found 489.3 (M+1)+; Retention time: 1.57 minutes (3 minutes run). ^1H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.29 (s, 1H), 7.73 (d, J = 7.3 Hz, 1H), 7.69 - 7.60 (m, 3H), 7.59 - 7.51 (m, 2H), 7.41 (s, 2H), 7.38 - 7.29 (m, 2H), 7.10 (d, J = 7.3 Hz, 1H) ppm.

EXAMPLE 22

Preparation of 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide (**13**)



[00255] 2-Fluoro-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide (130 mg, 0.36 mmol), 4-fluoro-2-methoxy-phenol (204.5 μL, 1.8 mmol) and Cs_2CO_3 (584.5 mg, 1.8 mmol) in NMP (1 mL) was stirred at 90 °C for 4 hours. The reaction mixture was poured into 1N HCl and extracted with ethyl acetate (3x). The organics were combined, washed with water, brine, dried with Na_2SO_4 and evaporated to dryness. Purification by reverse-phase HPLC using a gradient of (1-99% ACN in water (HCl modifier)) gave 2-(4-fluoro-2-methoxy-phenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide (**13**) (25.6 mg, 14%) as a white solid. ESI-MS m/z calc. 484.07, found 485.3 (M+1)+; Retention time: 1.61 minutes (3 minutes run). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.33 (s, 1H), 7.79 - 7.72 (m, 1H), 7.61 - 7.48 (m, 4H), 7.40 (s, 2H), 7.20 (dd, J = 8.9, 5.9 Hz, 1H), 7.14 (dd, J = 10.7, 2.9 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 6.84 (td, J = 8.4, 2.8 Hz, 1H), 3.77 (s, 3H) ppm.

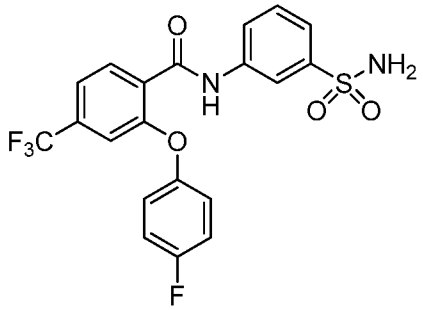
[00256] Following a similar procedure as described above for compound (**13**), the following compounds were prepared from 2-fluoro-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide and a phenol.

Cmpd. No.	**Product name**	**Phenol**
12	2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide	4-fluoro-2-methylphenol
57	2-(2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide	2-methoxyphenol
58	2-(4-chloro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-6-	4-chloro-2-methylphenol

	(trifluoromethyl)benzamide	
59	2-(3-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide	3-fluoro-2-methylphenol
60	N-(3-sulfamoylphenyl)-2-(4-(trifluoromethoxy)phenoxy)-6-(trifluoromethyl)benzamide	4-(trifluoromethoxy)phenol
61	2-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide	3-fluoro-4-methoxyphenol
74	2-(2-chlorophenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide	2-chlorophenol
75	2-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide	2-chloro-4-methoxyphenol

EXAMPLE 23

Preparation of 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide (**1**)



[00257] 2-Fluoro-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide (32.2 mg, 0.1 mmol), 4-fluorophenol (112.1 mg, 1 mmol) were dissolved in DMF (1 mL). Cs_2CO_3 (325.8 mg, 1 mmol) was added and the reactions was heated at 100 °C for 1 hour. The reaction was filtered and purified by reverse phase preparative HPLC utilizing a gradient of 10-99% acetonitrile in water (HCl as a modifier) to yield 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide (**1**) (25.6 mg, 56%). ESI-MS m/z calc. 454.06, found 455.3 (M+1)+; Retention time: 1.96 minutes (3 minutes run). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.34 - 8.24 (m, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.82 - 7.72 (m, 1H), 7.64 (dd, J = 7.9, 0.8 Hz, 1H), 7.60 - 7.47 (m, 2H), 7.40 (s, 2H), 7.32 - 7.25 (m, 2H), 7.25 - 7.18 (m, 2H), 7.15 (s, 1H) ppm.

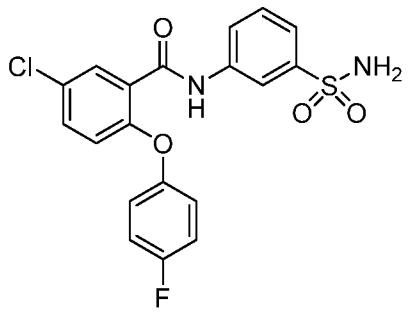
[00258] Following a similar procedure as described above for compound (**1**), the following compounds were prepared starting from 2-fluoro-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide and the following phenols.

Cmpd. No.	Product name	Phenol
2	2-(2,4-difluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide	2,4-difluorophenol
14	2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide	4-fluoro-2-methoxyphenol
18	2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide	4-fluoro-2-methylphenol
42	2-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide	4-chloro-2-methoxyphenol
43	2-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide	3-fluoro-4-methoxyphenol
44	2-(2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide	2-methoxyphenol
45	2-(4-ethoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide	4-ethoxyphenol
46	2-(2-propoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide	2-(2-propoxy)phenol
47	N-(3-sulfamoylphenyl)-2-(o-tolyloxy)-4-(trifluoromethyl)benzamide	2-methylphenol
48	2-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide	2-chloro-4-methoxyphenol
49	2-(4-methoxy-2-methylphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide	4-methoxy-2-methylphenol
50	2-(2,4-dimethoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide	2,4-dimethoxyphenol
51	N-(3-sulfamoylphenyl)-2-(4-(trifluoromethoxy)phenoxy)-4-(trifluoromethyl)benzamide	4-(trifluoromethoxy)phenol

52	2-(3-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide	3-fluoro-2-methoxyphenol
53	2-(4-isopropoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide	4-isopropoxyphenol
67	2-(3-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide	3-chloro-4-methoxyphenol
68	2-(3-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide	3-chloro-2-methoxyphenol
73	2-(2-chlorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide	2-chlorophenol

EXAMPLE 24

Preparation of 5-chloro-2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide (**5**)



[00259] 5-chloro-2-fluoro-N-(3-sulfamoylphenyl)benzamide (32.8 mg, 0.1 mmol), 4-fluorophenol (35.8 mg, 0.3 mmol) were dissolved in NMP (0.5 mL). Cs_2CO_3 (98 mg, 0.3 mmol) was added and the reactions was heated at 90 °C for 6 hour. The reaction was filtered and purified by reverse phase preparative HPLC utilizing a gradient of 10-99% acetonitrile in water (HCl as a modifier) to yield 5-chloro-2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide (**5**) (10.2 mg, 24%). ESI-MS m/z calc. 420.03, found 421.1 (M+1)+; Retention time: 1.70 minutes (3 minutes run).

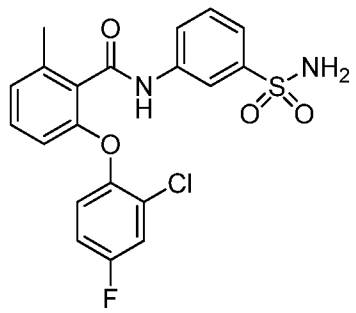
[00260] Following a similar procedure as described above for compound (**5**), the following compounds were prepared.

Cmpd. No.	**Product name**	**Aryl fluoride**	**Phenol**

16	5-chloro-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide	5-chloro-2-fluoro-N-(3-sulfamoylphenyl)benzamide	4-fluoro-2-methoxyphenol
17	5-chloro-2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide	5-chloro-2-fluoro-N-(3-sulfamoylphenyl)benzamide	2-chloro-4-fluorophenol
20	5-chloro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide	5-chloro-2-fluoro-N-(3-sulfamoylphenyl)benzamide	4-fluoro-2-methylphenol

EXAMPLE 25

Preparation of 2-(2-chloro-4-fluorophenoxy)-6-methyl-N-(3-sulfamoylphenyl)benzamide (**38**)



[00261] To a solution of 2-fluoro-6-methyl-benzaldehyde (1.1 g, 7.75 mmol) and 2-chloro-4-fluoro-phenol (817.7 µL, 7.75 mmol) in DMF (9.2 mL) was added cesium carbonate (2.5 g, 7.75 mmol) and the mixture was heated at 100 °C for 1 hour. The mixture was cooled to room temperature before it was diluted with ethyl acetate and water. The layers were separated and the aqueous layer was extracted with ethyl acetate (3x). The combined organics were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography using a gradient of ethyl acetate in hexanes (0-100%) to yield 2-(2-chloro-4-fluoro-phenoxy)-6-methyl-benzaldehyde (1.05 g, 51%). ESI-MS m/z calc. 264.03, found 265.1 (M+1)+; Retention time: 2.02 minutes (3 minutes run).

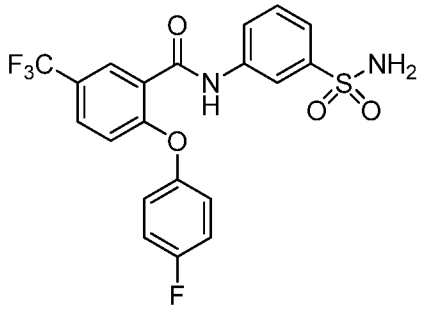
[00262] To a solution of 2-(2-chloro-4-fluoro-phenoxy)-6-methyl-benzaldehyde (1.05 g, 3.97 mmol) in *t*-BuOH (10.50 mL), water (6.6 mL) and acetonitrile (6.6 mL) was added sodium dihydrogen phosphate (745.7 µL, 11.90 mmol), 2-methylbut-2-ene (2.1 mL, 19.83 mmol) and sodium chlorite (1.08 g, 11.90 mmol). The reaction mixture was stirred at 25 °C for 1h. The reaction mixture was acidified with 1N HCl and was diluted with ethyl acetate. Sodium sulfite was added to remove the faint yellow color. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3x). The organics were combined, washed with brine, dried over sodium sulfate, filtered and concentrated to give 2-

(2-chloro-4-fluoro-phenoxy)-6-methyl-benzoic acid (1.06 g, 95%). ESI-MS m/z calc. 280.03, found 281.5 (M+1)+; Retention time: 1.7 minutes (3 minutes run).

[00263] DMF (1.4 μL, 0.018 mmol) was added to a mixture of 2-(2-chloro-4-fluoro-phenoxy)-6-methyl-benzoic acid (100 mg, 0.36 mmol), CH_2Cl_2 (2.0 mL) and $SOCl_2$ (33.8 μL, 0.46 mmol) at room temperature. The mixture was allowed to stir for 1.5 hours before it was concentrated under reduced pressure. The residue was placed under high vacuum for 30 minutes before it was taken up in CH_2Cl_2 (2.0 mL) and added to a mixture of 3-aminobenzenesulfonamide (92.0 mg, 0.53 mmol), Et_3N (86.5 μL, 1.07 mmol) and CH_2Cl_2 (2.0 mL) at room temperature. The mixture was allowed to stir for 2h at room temperature before it was partitioned between 1N HCl and CH_2Cl_2. The layers were separated and the organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was subjected to preparatory-HPLC (10-90% ACN/water with 0.01% HCl) to give 2-(2-chloro-4-fluoro-phenoxy)-6-methyl-N-(3-sulfamoylphenyl)benzamide (**38**) (6.5 mg, 4%). ESI-MS m/z calc. 434.05, found 435.5 (M+1)+; Retention time: 1.72 minutes (3 minutes run). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 8.41 - 8.36 (m, 1H), 7.76 (dt, J = 7.1, 2.0 Hz, 1H), 7.63 - 7.51 (m, 3H), 7.39 (s, 2H), 7.34 - 7.25 (m, 3H), 7.12 - 7.07 (m, 1H), 6.61 (t, J = 8.0 Hz, 1H), 2.35 (s, 3H) ppm.

EXAMPLE 26

Preparation of 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide (**3**)

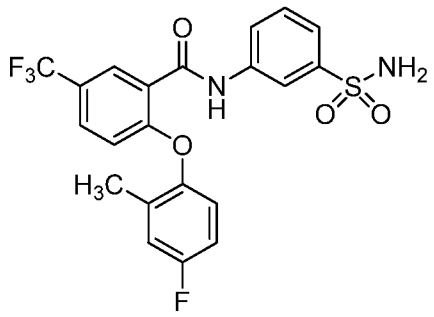


[00264] A mixture of 2-fluoro-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide (9.0 g, 24.8 mmol), 4-fluorophenol (8.4 g, 74.5 mmol), cesium carbonate (24.3 g, 74.5 mmol) and DMF (225.0 mL) was heated at 100 °C for 0.5 hours. The mixture was cooled to room temperature before it was partitioned between ethyl acetate and water. The layers were separated and the aqueous layer was extracted with ethyl acetate (3x). The combined organics were washed with saturated aqueous NH_4Cl, water and brine. The

organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (0-100% ethyl acetate/hexanes) to give an off-white solid. The solid was slurried with hexane, then filtered. That solid was slurried in diethyl ether and filtered (2x). The solid was placed under vacuum at 55 °C for 1 hour to give 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide (**3**) (8.6 g, 77%). ESI-MS m/z calc. 454.06, found 455.5 (M+1)+; Retention time: 1.87 minutes (3 minutes run). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H), 8.30 (s, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.82 (ddd, J = 8.9, 4.8, 2.2 Hz, 2H), 7.61 - 7.49 (m, 2H), 7.40 (s, 2H), 7.35 - 7.23 (m, 4H), 7.00 (d, J = 8.7 Hz, 1H) ppm.

EXAMPLE 27

Preparation of 2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide (**25**)

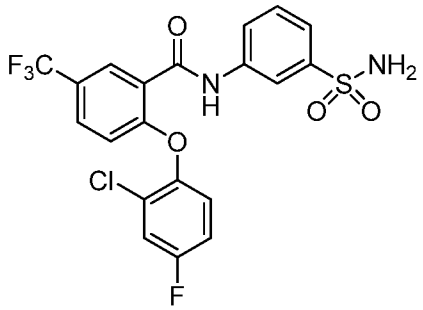


[00265] To a mixture of 2-fluoro-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide (10 g, 27.60 mmol) in DMF (55.00 mL) was added 4-fluoro-2-methyl-phenol (3.7 g, 28.98 mmol) and cesium carbonate (10.8 g, 33.12 mmol) and the mixture heated at 100 °C for 1h. The mixture was cooled to ambient temperature and diluted with 300 mL of ice water. The mixture was acidified with 6N HCl and diluted to a volume of 400 mL with water. The slurry was diluted with 400 mL of ethyl acetate and the organic phase separated. The organic phase was washed with 400 mL of water and then 400 mL of brine. The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude solid was diluted with 100 mL of acetonitrile and heated until homogeneous. Mixture stirred at 25 °C, the precipitate was collected by filtration and washed with 25 mL of acetonitrile to yield 2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide (**25**) (4.14 g, 32%). ESI-MS m/z calc. 468.08, found 469.20 (M+1)+; Retention time: 1.81 minutes (3 minutes run). ^{1}H NMR (400 MHz, DMSO-d_6) δ

10.83 (s, 1H), 8.33 (s, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.81 (m, 2H), 7.56 (m, 2H), 7.40 (s, 2H), 7.23 (ddd, J = 13.9, 9.1, 4.0 Hz, 2H), 7.14 (td, J = 8.6, 3.1 Hz, 1H), 6.82 (d, J = 8.7 Hz, 1H), 2.15 (s, 3H) ppm.

EXAMPLE 28

Preparation of 2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide (**26**)



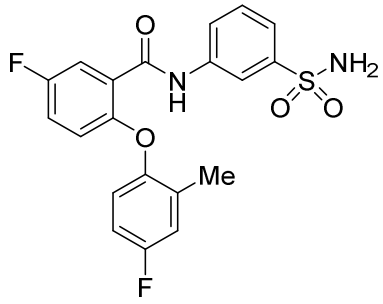
[00266] A mixture of 2-fluoro-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide (15 g, 41.40 mmol), 2-chloro-4-fluoro-phenol (17.35 g, 118.4 mmol), cesium carbonate (40.47 g, 124.20 mmol) and DMF (375.0 mL) was heated at 100 °C for 1 hour and 15 minutes. The mixture was cooled to room temperature and filtered using ethyl acetate. Water was added to the filtrate. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organics were washed with saturated aqueous solution of NH_4Cl, water and brine. The organics were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified silica gel chromatography utilizing a gradient of ethyl acetate in dichloromethane (0-10%). The fractions containing the desired product were concentrated and the resulting solid slurried in ether and hexanes and filtered. The solvent was evaporated under reduced pressure to yield 2-(2-chloro-4-fluoro-phenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide (**26**) (10.35 g, 50%) as a light pink solid. ESI-MS m/z calc. 488.02, found 489.2 (M+1)+; Retention time: 2.03 minutes (3 minutes run). ^1H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 8.37 - 8.27 (m, 1H), 8.04 (d, J = 2.1 Hz, 1H), 7.92 - 7.74 (m, 2H), 7.69 (dd, J = 8.4, 3.0 Hz, 1H), 7.63 - 7.50 (m, 2H), 7.50 - 7.28 (m, 4H), 6.92 (d, J = 8.7 Hz, 1H) ppm.

[00267] Following a similar procedure as described above for compound (**26**), the following compounds were prepared starting from 2-fluoro-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide and the phenols listed below.

Cmpd. No.	Product name	Phenol
32	N-(3-sulfamoylphenyl)-2-(o-tolyloxy)-5-(trifluoromethyl)benzamide	o-cresol
34	2-(2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide	2-methoxyphenol
22	2-(4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide	4-methoxyphenol
24	2-(4-chlorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide	4-Chlorophenol
6	2-(2,4-difluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide	2,4-difluorophenol
23	2-(4-ethoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide	4-ethoxyphenol
30	2-(4-chloro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide	4-chloro-2-methylphenol
29	2-(3-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide	3-fluoro-2-methoxyphenol
27	2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide	4-fluoro-2-methoxyphenol
28	2-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide	3-fluoro-4-methoxyphenol
37	2-(4-isopropoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide	4-isopropoxyphenol
36	2-(2,4-dimethoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide	2,4-dimethoxyphenol
35	2-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide	4-chloro-2-methoxyphenol
31	2-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide	2-chloro-4-methoxyphenol
41	2-(4-(difluoromethoxy)phenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide	4-(difluoromethoxy)phenol
39	N-(3-sulfamoylphenyl)-2-(4-(trifluoromethoxy)phenoxy)-5-(trifluoromethyl)benzamide	4-(trifluoromethoxy)phenol

EXAMPLE 29

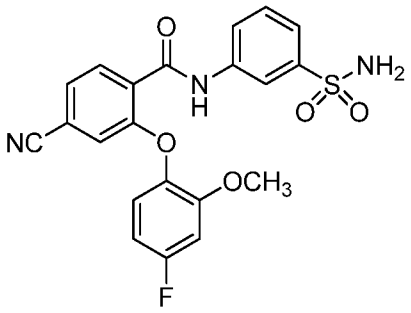
Preparation of 5-fluoro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide (**21**)



[00268] To a solution of 2,5-difluoro-N-(3-sulfamoylphenyl)benzamide (200 mg, 0.64 mmol) in DMF (2 mL) was added 4-fluoro-2-methyl-phenol (72.99 µL, 0.64 mmol) and cesium carbonate (1.0 g, 3.2 mmol) and the mixture was heated at 100 °C for 3 hours. The reaction was cooled to 25 °C, diluted with ethyl acetate and poured over water. The 2 layers were separated and the aqueous layer was extracted with ethyl acetate (2x). The organics were combined, dried over $MgSO_4$, filtered and evaporated to yield a red oil that was purified by column chromatography using a gradient of ethyl acetate and hexanes to yield 5-fluoro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide (**21**) (7.2 mg, 3%).

EXAMPLE 30

Preparation of 4-cyano-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide (**10**)



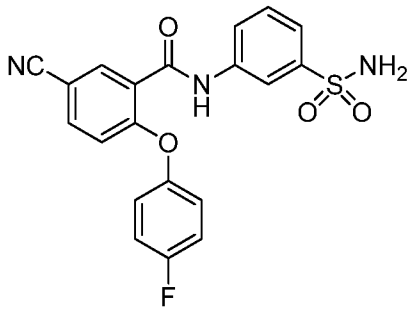
[00269] To a solution of 4-cyano-2-fluoro-N-(3-sulfamoylphenyl)benzamide (19.2 mg, 0.06 mmol) and 4-fluoro-2-methoxyphenol (42.6 mg, 0.3 mmol) in NMP (0.5 mL) was added Cs_2CO_3 (97.7 mg, 0.3 mmol) and the mixture was stirred at 90 °C for 4 hours. The reaction was filtered and purified by reverse phase HPLC using a gradient of acetonitrile in water (1-99%) to give 4-cyano-2-(4-fluoro-2-methoxy-phenoxy)-N-(3-sulfamoylphenyl)benzamide. ESI-MS m/z calc. 441.08, found 442.3 (M+1)+; Retention time: 1.53 minutes (3 minutes run).

[00270] Following a similar procedure as described above for compound (**10**), the following compounds were prepared starting from 4-cyano-2-fluoro-N-(3-sulfamoylphenyl)benzamide and the phenols listed below.

Cmpd No.	**Product name**	**Phenol**
4	2-(2-chloro-4-fluoro-phenoxy)-4-cyano-N-(3-sulfamoylphenyl)benzamide	2-chloro-4-fluorophenol
9	4-cyano-2-(4-fluoro-2-methyl-phenoxy)-N-(3-sulfamoylphenyl)benzamide	4-fluoro-2-methyl-phenol

EXAMPLE 31

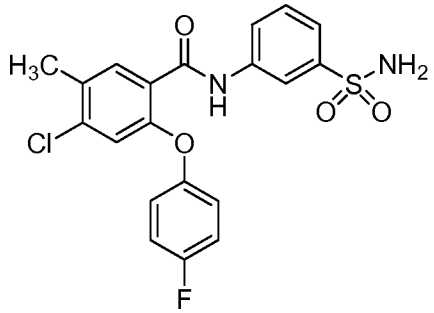
Preparation of 2-(2-chloro-4-fluorophenoxy)-5-cyano-N-(3-sulfamoylphenyl)benzamide (**11**)



[00271] To a solution of 5-cyano-2-fluoro-N-(3-sulfamoylphenyl)benzamide (31.9 mg, 0.10 mmol) and 2-chloro-4-fluorophenol (44.0 mg, 0.30 mmol) in NMP (0.5 mL) was added Cs_2CO_3 (97.7 mg, 0.30 mmol) and the mixture was stirred at 90 °C for 4 hours. The reaction was filtered and purified by reverse phase HPLC using a gradient of acetonitrile in water (1-99%) using HCl as a modifier to yield 2-(2-chloro-4-fluoro-phenoxy)-5-cyano-N-(3-sulfamoylphenyl)benzamide (**11**) (5.8 mg, 13%). ESI-MS m/z calc. 445.03, found 446.1 (M+1)+; Retention time: 1.57 minutes (3 minutes run). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.84 (s, 1H), 8.33 (s, 1H), 8.20 (d, J = 2.0 Hz, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.81 (d, J = 6.9 Hz, 1H), 7.69 (dd, J = 8.3, 2.8 Hz, 1H), 7.60 - 7.54 (m, 2H), 7.48 (dd, J = 9.1, 5.2 Hz, 1H), 7.44 - 7.34 (m, 3H), 6.88 (d, J = 8.7 Hz, 1H) ppm.

EXAMPLE 32

Preparation of 4-chloro-2-(4-fluorophenoxy)-5-methyl-N-(3-sulfamoylphenyl)benzamide (**7**)



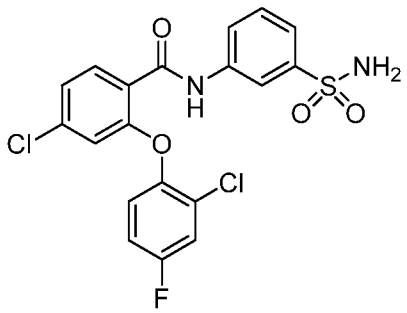
[00272] To a solution of 5-bromo-4-chloro-2-fluoro-N-(3-sulfamoylphenyl)benzamide (122.3 mg, 0.3 mmol) and 4-fluorophenol (100.9 mg, 0.9 mmol) in N,N-dimethylformamide (3 mL) was added cesium carbonate (293.2 mg, 0.9 mmol) and the reaction was heated at 100 °C for 2 hours. The reaction was filtered and purified by reverse phase preparative chromatography utilizing a gradient of 20-99% acetonitrile in water

containing HCl as a modifier to yield 5-bromo-4-chloro-2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide (59.5 mg, 40%).

[00273] To 5-bromo-4-chloro-2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide (44 mg, 0.09 mmol), methylboronic acid (7.9 mg, 0.13 mmol), tetrakis(triphenylphosphine)palla-dium (0) (5.3 mg, 0.004 mmol) and 1,2-dimethoxyethane (500 μL) was added sodium carbonate (132.1 μL of 2 M solution, 0.26 mmol) and the reaction was heated at 80 °C for 65 hours. The reaction was filtered and the solvent was evaporated. The crude product was purified by reverse phase LCMS using acetonitrile and water containing HCl as a modifier to yield 4-chloro-2-(4-fluorophenoxy)-5-methyl-N-(3-sulfamoylphenyl)benzamide (**7**) (12.1 mg, 29%) as a yellow solid. ESI-MS m/z calc. 434.05, found 435.15 (M+1)+; Retention time: 1.8 minutes (3 minutes run). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.65 (s, 1H), 8.30 - 8.24 (m, 1H), 7.81 - 7.72 (m, 1H), 7.68 (s, 1H), 7.58 - 7.48 (m, 2H), 7.38 (s, 2H), 7.29 - 7.18 (m, 2H), 7.18 - 7.09 (m, 2H), 6.98 (s, 1H), 2.36 (s, 3H) ppm.

EXAMPLE 33

Preparation of 4-chloro-2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide (**8**)



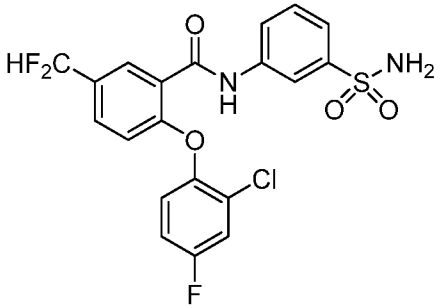
[00274] To a solution of 4-chloro-2-fluoro-N-(3-sulfamoylphenyl)benzamide (39.4 mg, 0.12 mmol) and 2-chloro-4-fluorophenol (52.8 mg, 0.36 mmol) in DMF (0.8 mL) was added cesium carbonate (117.3 mg, 0.36 mmol) and the reaction was heated at 100 °C for 1 hour. The reaction was filtered and purified by reverse phase preparative chromatography utilizing a gradient of 10-99% acetonitrile in water containing HCl as a modifier to yield 4-chloro-2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide (**8**) (1.7 mg, 3%). ESI-MS m/z calc. 454.00, found 455.3 $(M+1)^+$; Retention time: 1.73 minutes (3 minutes run).

[00275] Following a similar procedure as described above for compound (**8**), the following compounds were prepared starting from 4-chloro-2-fluoro-N-(3-sulfamoylphenyl)benzamide and the phenols listed below.

Cmpd. No.	Product name	Phenol
15	4-chloro-2-(4-fluoro-2-methoxy-phenoxy)-N-(3-sulfamoylphenyl)benzamide	4-fluoro-2-methoxy-phenol
19	4-chloro-2-(4-fluoro-2-methyl-phenoxy)-N-(3-sulfamoylphenyl)benzamide	4-fluoro-2-methyl-phenol
84	4-chloro-2-(2,4-dimethoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide	2,4-dimethoxyphenol
85	4-chloro-2-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide	4-chloro-2-methoxyphenol
86	4-chloro-2-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide	2-chloro-4-methoxyphenol
87	4-chloro-2-(4-isopropoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide	4-isopropoxyphenol

EXAMPLE 34

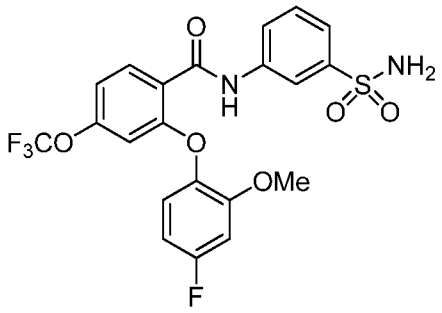
Preparation of 2-(2-chloro-4-fluorophenoxy)-5-(difluoromethyl)-N-(3-sulfamoylphenyl)benzamide (**40**)



[00276] 5-(Difluoromethyl)-2-fluoro-N-(3-sulfamoylphenyl)benzamide (75 mg, 0.22 mmol), 2-chloro-4-fluoro-phenol (95.7 mg, 0.65 mmol) and cesium carbonate (212.9 mg, 0.65 mmol) in NMP (0.75 mL) was stirred at 90 °C for 2 hours. The reaction mixture was diluted with MeOH, filtered and purification by reverse phase HPLC using a gradient of acetonitrile in water (1-99%) and HCl as a modifier gave 2-(2-chloro-4-fluorophenoxy)-5-(difluoromethyl)-N-(3-sulfamoylphenyl)benzamide (**40**) (56 mg, 53%) as a white solid. ESI-MS m/z calc. 470.03, found 471.3 $(M+1)^+$; Retention time: 1.63 minutes (3 minute run). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.77 (s, 1H), 8.32 (s, 1H), 7.87 (s, 1H), 7.85 - 7.78 (m, 1H), 7.72 - 7.64 (m, 2H), 7.60 - 7.53 (m, 2H), 7.39 (s br, 3H), 7.35 (d, J = 8.1 Hz, 1H), 7.10 (t, J = 55.8 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H) ppm.

EXAMPLE 35

Preparation of 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide (**54**)



[00277] To 2-fluoro-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide (75.7 mg, 0.2 mmol), 4-fluoro-2-methoxyphenol (68.3 µl, 0.6 mmol), cesium carbonate (195.5 mg, 0.6 mmol) and N-methylpyrrolidinone (2 mL) were added and the reaction was stirred at 100 °C for 30 minutes to 2 hours. The reaction was filtered and mixture was purified by reverse phase preparative chromatography utilizing a gradient of 10-99% acetonitrile in water containing HCl as a modifier to yield 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide (**54**) (27.8 mg, 27%). ESI-MS m/z calc. 500.07, found 501.2 (M+1)+; Retention time: 1.99 minutes (3 minutes run). ^{1}H-NMR (DMSO-d_6) δ 10.68 (s, 1H), 8.37 - 8.30 (m, 1H), 7.84 - 7.79 (m, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.60 - 7.50 (m, 2H), 7.40 (s, 2H), 7.37 - 7.28 (m, 1H), 7.23 - 7.11 (m, 2H), 6.93 - 6.82 (m, 1H), 6.58 - 6.50 (m, 1H), 3.75 (s, 3H) ppm.

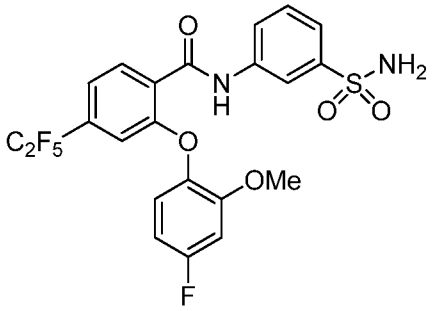
[00278] The following compounds were prepared using a similar experimental procedure to compound (**54**) above starting from 2-fluoro-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide and the phenols listed below.

Cmpd No.	Product name	Phenol
55	2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide	4-fluorophenol
56	2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide	2-chloro-4-fluorophenol
62	2-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide	2-chloro-4-methoxyphenol
63	2-(2-chlorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide	2-chlorophenol
64	2-(2-(difluoromethoxy)phenoxy)-N-(3-	2-

	sulfamoylphenyl)-4-(trifluoromethoxy)benzamide	(difluoromethoxy)phenol
65	2-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide	4-chloro-2-methoxyphenol
66	2-(3-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide	3-chloro-2-methoxyphenol

EXAMPLE 36

Preparation of 2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide (**70**)



[00279] 2-Fluoro-4-(1,1,2,2,2-pentafluoroethyl)-N-(3-sulfamoylphenyl)benzamide (34.2 mg, 0.1 mmol), the 2-methoxy-4-fluorophenol (34.2 µl, 0.3 mmol) and Cs_2CO_3 (97.8 mg, 0.3 mmol) in NMP (0.4 mL) was stirred at 80°C for 2 hours. Purification by HPLC using a gradient of 1-99% acetonitrile in water, using HCl as a modifier, gave 2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide (**70**) (17.8 mg, 33%). ESI-MS m/z calc. 534.07, found 535.3 (M+1)+; Retention time: 1.78 minutes (3 minutes run).

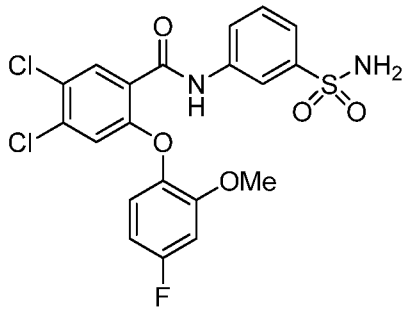
[00280] The following compounds were prepared using a similar experimental procedure as used for compound (**70**) above starting from 2-fluoro-4-(1,1,2,2,2-pentafluoroethyl)-N-(3-sulfamoylphenyl)benzamide and the phenols listed below.

Cmpd No.	**Product name**	**Phenol**
69	2-(4-fluorophenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide	4-fluorophenol
71	2-(4-chloro-2-methoxyphenoxy)-4-	4-chloro-2-

	(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide	methoxyphenol
72	2-(2-chloro-4-methoxyphenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide	2-chloro-4-methoxyphenol

EXAMPLE 37

Preparation of 4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide (**77**)



[00281] 4,5-Dichloro-2-fluoro-N-(3-sulfamoylphenyl)benzamide (50 mg, 0.14 mmol), 4-fluoro-2-methoxyphenol (17.3 µl, 0.15 mmol), and K_2CO_3 (57.1 mg, 0.41 mmol) were combined in DMF (0.5 mL) and heated at 75 °C for 12 hours. The reaction mixture was filtered and purified by reverse phase HPLC using a gradient of acetonitrile in water 10-99% and 5 mM HCl in the mobile phase to provide 4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide (**77**) (7.5 mg, 11%). ESI-MS m/z calc. 484.01, found 485.3 (M+1)+; Retention time: 1.74 minutes (3 minutes run). ^{1}H NMR (400 MHz, DMSO-d6) δ 10.70 (s, 1H), 8.33 - 8.26 (m, 1H), 7.93 (s, 1H), 7.80 (dt, J = 6.4, 2.3 Hz, 1H), 7.60 - 7.49 (m, 2H), 7.40 (s, 2H), 7.29 (dd, J = 8.8, 5.8 Hz, 1H), 7.14 (dd, J = 10.7, 2.9 Hz, 1H), 6.89 - 6.79 (m, 2H), 3.76 (s, 3H) ppm.

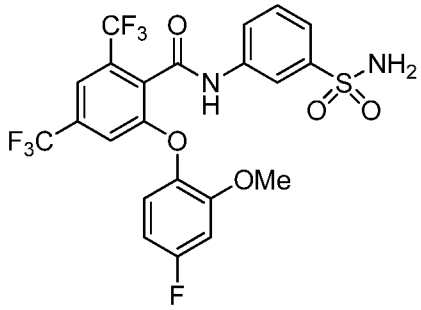
[00282] The following compounds were prepared using a similar experimental procedure as for compound (**77**) above starting from 4,5-dichloro-2-fluoro-N-(3-sulfamoylphenyl)benzamide and the phenols listed below.

Cmpd No.	**Product name**	**Phenol**
76	4,5-dichloro-2-(2,4-dimethoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide	2,4-dimethoxyphenol
78	4,5-dichloro-2-(4-fluorophenoxy)-N-(3-	4-fluorophenol

	sulfamoylphenyl)benzamide	
79	4,5-dichloro-2-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide	3-fluoro-4-methoxyphenol
80	4,5-dichloro-2-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide	4-chloro-2-methoxyphenol
81	4,5-dichloro-2-(2-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide	2-fluoro-4-methoxyphenol
82	4,5-dichloro-2-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide	2-chloro-4-methoxyphenol
83	4,5-dichloro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide	4-fluoro-2-methylphenol

EXAMPLE 38

Preparation of 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide (**89**)



[00283] To 2-Fluoro-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide (70 mg, 0.16 mmol) and 4-fluoro-2-methoxyphenol (20.4 μL, 0.18 mmol) in DMF (68.4 μL) was added K_2CO_3 (67.5 mg, 0.49 mmol). The reaction was stirred at 70°C for 2 hours, then at 100°C for 1 hour. The reaction was cooled to room temperature, filtered and purified by reverse phase HPLC using a gradient of acetonitrile in water (10-99%) to yield 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide (**89**) (44.9 mg, 50%). ESI-MS m/z calc. 552.06, found 553.2 (M+1)+; Retention time: 1.87 minutes (3 minutes run).

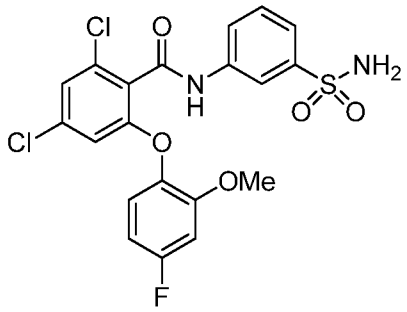
[00284] The following compounds were prepared using a similar experimental procedure as for compound (**89**) above starting from 2-fluoro-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide and the phenols listed below.

Cmpd No.	**Product name**	**Phenol**
88	2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-	4-fluorophenol

	4,6-bis(trifluoromethyl)benzamide	
90	2-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide	3-fluoro-4-methoxyphenol
91	2-(2-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide	2-fluoro-4-methoxyphenol
92	2-(5-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide	5-fluoro-2-methoxyphenol
93	2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide	4-fluoro-2-methylphenol

EXAMPLE 39

Preparation of 2,4-dichloro-6-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide (**95**)



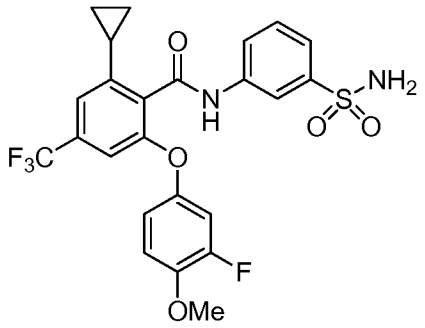
[00285] A mixture of 2,4-dichloro-6-fluoro-N-(3-sulfamoylphenyl)benzamide (36.3 mg, 0.1 mmol), 4-fluoro-2-methoxyphenol (34.2 μL, 0.30 mmol) and Cs_2CO_3 (97.7 mg, 0.3 mmol) in NMP (0.4 mL) was stirred for 1 hour at 80 °C. The reaction mixture was diluted with methanol, filtered and purified by reverse phase HPLC using a gradient of acetonitrile/water (1-99%) and HCl as a modifier to give 2,4-dichloro-6-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide (**95**) (6.5 mg, 13%) as a white solid. ESI-MS m/z calc. 484.01, found 485.5 (M+1)+; Retention time: 1.58 minutes (3 minutes run). ^{1}H NMR (400 MHz, DMSO-d6) δ 11.02 (s, 1H), 8.34 (s, 1H), 7.81 - 7.74 (m, 1H), 7.61 - 7.53 (m, 2H), 7.48 (d, J = 1.8 Hz, 1H), 7.41 (s, 2H), 7.21 (dd, J = 8.8, 5.8 Hz, 1H), 7.15 (dd, J = 10.6, 2.9 Hz, 1H), 6.89 - 6.81 (m, 1H), 6.60 (d, J = 1.8 Hz, 1H), 3.78 (s, 3H) ppm.

[00286] The following compounds were prepared using a similar experimental procedure as for compound (**95**) above starting from 2,4-dichloro-6-fluoro-N-(3-sulfamoylphenyl)benzamide and the phenols listed below.

Cmpd No.	Product name	Phenol
94	2,4-dichloro-6-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide	4-fluorophenol
96	2,4-dichloro-6-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide	4-fluoro-2-methylphenol
97	2,4-dichloro-N-(3-sulfamoylphenyl)-6-(4-(trifluoromethoxy)phenoxy)benzamide	4-(trifluoromethoxy)phenol
98	2,4-dichloro-6-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide	4-chloro-2-methoxyphenol
99	2,4-dichloro-6-(2-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide	2-fluoro-4-methoxyphenol

EXAMPLE 40

Preparation of 2-cyclopropyl-6-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide (**100**)



[00287] To a mixture of 2-cyclopropyl-6-fluoro-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide (20 mg, 0.08 mmol) and 3-fluoro-4-methoxyphenol (17.7 mg, 0.12 mmol) in DMF (0.5 mL) was added K_2CO_3 (41.2 mg, 0.3 mmol) and the reaction was stirred at 100°C for 2 hours, then at 80°C overnight. The reaction was cooled to room temperature, filtered and purified by reverse phase HPLC using a gradient of acetonitrile in water (1-99%) and HCl as a modifier to yield 2-cyclopropyl-6-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide (**100**) (3.69 mg, 9%). ESI-MS m/z calc. 524.10, found 525.2 (M+1)+; Retention time: 1.50 minutes (3 minutes run).

EXAMPLE 41

[00288] Analytical data for the compounds of the present invention is provided below in Table 2. Mass Spec (e.g., M+1 data in Table 2), final purity and retention times were determined by reverse phase HPLC using a Kinetix C18 column (50 × 2.1 mm, 1.7 μm particle) from Phenomenex (pn: 00B-4475-AN)), and a dual gradient run from 1-99% mobile phase B over 3 minutes. Mobile phase A = H_20 (0.05 % CF_3CO_2H). Mobile phase B = CH_3CN (0.05 % CF_3CO_2H). Flow rate = 2 mL/min, injection volume = 3 μL, and column temperature = 50 °C.

[00289] **Table 2**. Analytical Data

Cmpd. No	**LCMS Retention Time in minutes**	**(M+1)**	**^{1}H-NMR (400 MHz)**
1	1.96	455.3	(DMSO-d_6) δ 10.84 (s, 1H), 8.34 - 8.24 (m, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.82 - 7.72 (m, 1H), 7.64 (dd, J = 7.9, 0.8 Hz, 1H), 7.60 - 7.47 (m, 2H), 7.40 (s, 2H), 7.32 - 7.25 (m, 2H), 7.25 - 7.18 (m, 2H), 7.15 (s, 1H) ppm.
2	1.95	473.2	
3	1.86	455.5	(DMSO-d_6) δ 10.81 (s, 1H), 8.30 (s, 1H), 8.01 (d, J = 2.3 Hz, 1H), 7.86 - 7.78 (m, 2H), 7.59 - 7.53 (m, 2H), 7.39 (s, 2H), 7.35 - 7.24 (m, 4H), 7.00 (d, J = 8.7 Hz, 1H) ppm.
4	1.57	446.3	
5	1.71	421.1	
6	1.91	473.3	
7	1.8	435.15	(DMSO-d_6) δ 10.65 (s, 1H), 8.30 - 8.24 (m, 1H), 7.81 - 7.72 (m, 1H), 7.68 (s, 1H), 7.58 - 7.48 (m, 2H), 7.38 (s, 2H), 7.29 - 7.18 (m, 2H), 7.18 - 7.09 (m, 2H), 6.98 (s, 1H), 2.36 (s, 3H) ppm.
8	1.73	455.3	
9	1.58	426.3	
10	1.53	442.3	
11	1.57	446.1	(DMSO-d_6) δ 10.84 (s, 1H), 8.33 (s, 1H), 8.20 (d, J = 2.0 Hz, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.81 (d, J = 6.9 Hz, 1H), 7.69 (dd, J = 8.3, 2.8 Hz, 1H), 7.60 - 7.54 (m, 2H), 7.48 (dd, J = 9.1, 5.2 Hz, 1H), 7.44 - 7.34 (m, 3H), 6.88 (d, J = 8.7 Hz, 1H) ppm.
12	1.66	469.3	

Cmpd. No	LCMS Retention Time in minutes	(M+1)	^{1}H-NMR (400 MHz)
13	1.61	485.3	(DMSO-d_6) δ 10.98 (s, 1H), 8.33 (s, 1H), 7.79 - 7.72 (m, 1H), 7.61 - 7.48 (m, 4H), 7.40 (s, 2H), 7.20 (dd, J = 8.9, 5.9 Hz, 1H), 7.14 (dd, J = 10.7, 2.9 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 6.84 (td, J = 8.4, 2.8 Hz, 1H), 3.77 (s, 3H) ppm.
14	1.78	485.3	
15	1.74	451.1	
16	1.74	451.1	
17	1.76	455.3	
18	1.83	469.3	
19	1.81	435.3	
20	1.79	435.3	
21	1.85	419.1	(DMSO-d_6) δ 10.73 (s, 1H), 8.30 (s, 1H), 7.75 (m, 1H), 7.54 (m, 3H), 7.39 (s, 2H), 7.32 (m, 1H), 7.16 (dd, J = 9.4, 2.9 Hz, 1H), 7.04 (td, J = 8.6, 3.2 Hz, 1H), 6.97 (dd, J = 8.8, 5.1 Hz, 1H), 6.84 (dd, J = 9.1, 4.4 Hz, 1H), 2.18 (s, 3H) ppm.
22	1.76	467.2	
23	1.85	481.1	
24	1.82	471.2	
25	1.81	469.2	(DMSO-d_6) δ 10.83 (s, 1H), 8.33 (s, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.81 (m, 2H), 7.56 (m, 2H), 7.40 (s, 2H), 7.23 (ddd, J = 13.9, 9.1, 4.0 Hz, 2H), 7.14 (td, J = 8.6, 3.1 Hz, 1H), 6.82 (d, J = 8.7 Hz, 1H), 2.15 (s, 3H) ppm.
26	1.78	489.2	(DMSO-d_6) δ 10.84 (s, 1H), 8.32 (d, J = 1.6 Hz, 1H), 8.04 (d, J = 2.1 Hz, 1H), 7.82 (m, 2H), 7.69 (dd, J = 8.4, 3.0 Hz, 1H), 7.56 (m, 2H), 7.47 (dd, J = 9.1, 5.3 Hz, 1H), 7.37 (m, 3H), 6.92 (d, J = 8.7 Hz, 1H) ppm.
27	1.79	485.2	(DMSO-d_6) δ 10.74 (s, 1H), 8.33 (s, 1H), 7.97 (d, J = 2.2 Hz, 1H), 7.84 (m, 1H), 7.77 (dd, J = 8.9, 2.2 Hz, 1H), 7.56 (m, 2H), 7.40 (s, 2H), 7.35 (dd, J = 8.8, 5.9 Hz, 1H), 7.17 (dd, J = 10.7, 2.9 Hz, 1H), 6.88 (td, J = 8.4, 2.9 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 3.75 (s, 3H) ppm.
28	1.73	485.2	
29	1.74	485.1	
30	1.9	485.2	
31	1.81	501.1	
32	2.0	451.1	(DMSO-d_6) δ 10.82 (s, 1H), 8.32 (s, 1H), 8.01 (s,

Cmpd. No	LCMS Retention Time in minutes	(M+1)	^{1}H-NMR (400 MHz)
			1H), 7.81 (s, 2H), 7.56 (s, 2H), 7.26 (m, 6H), 6.82 (d, J = 8.3 Hz, 1H), 2.15 (s, 3H) ppm.
33	1.77	489.3	(DMSO-d_6) δ 11.02 (s, 1H), 8.32 - 8.25 (m, 1H), 7.73 (dt, J = 7.2, 2.0 Hz, 1H), 7.69 - 7.60 (m, 3H), 7.60 - 7.50 (m, 2H), 7.41 (s, 2H), 7.37 - 7.31 (m, 2H), 7.13 - 7.07 (m, 1H) ppm.
34	1.72	467.1	(DMSO-d_6) δ 10.74 (s, 1H), 8.33 (s, 1H), 7.98 (d, J = 2.1 Hz, 1H), 7.84 (m, 1H), 7.77 (dd, J = 8.9, 2.3 Hz, 1H), 7.56 (m, 2H), 7.40 (s, 2H), 7.31 (dd, J = 11.5, 4.6 Hz, 2H), 7.23 (m, 1H), 7.05 (td, J = 7.7, 1.5 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 3.74 (s, 3H) ppm.
35	1.82	501.1	(DMSO-d_6) δ 10.75 (s, 1H), 8.32 (s, 1H), 7.98 (d, J = 2.2 Hz, 1H), 7.83 (dt, J = 6.2, 2.4 Hz, 1H), 7.77 (dd, J = 8.9, 2.3 Hz, 1H), 7.56 (m, 2H), 7.40 (s, 2H), 7.31 (dd, J = 5.4, 2.9 Hz, 2H), 7.11 (dd, J = 8.5, 2.4 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 3.77 (s, 3H) ppm.
36	1.75	497.1	
37	1.88	495.1	
38	1.72	435.5	(DMSO-d_6) δ 10.83 (s, 1H), 8.41 - 8.36 (m, 1H), 7.76 (dt, J = 7.1, 2.0 Hz, 1H), 7.63 - 7.51 (m, 3H), 7.39 (s, 2H), 7.34 - 7.25 (m, 3H), 7.12 - 7.07 (m, 1H), 6.61 (t, J = 8.0 Hz, 1H), 2.35 (s, 3H) ppm.
39	2.16	521.3	(DMSO-d_6) δ 10.83 (s, 1H), 8.31 - 8.23 (m, 1H), 8.05 (d, J = 2.3 Hz, 1H), 7.87 (dd, J = 8.8, 2.2 Hz, 1H), 7.82 - 7.75 (m, 1H), 7.59 - 7.50 (m, 2H), 7.50 - 7.42 (m, 2H), 7.39 (s, 2H), 7.35 - 7.26 (m, 2H), 7.13 (d, J = 8.8 Hz, 1H) ppm.
40	1.63	471.3	(DMSO-d_6) δ 10.77 (s, 1H), 8.32 (s, 1H), 7.87 (s, 1H), 7.85 - 7.78 (m, 1H), 7.72 - 7.64 (m, 2H), 7.60 - 7.53 (m, 2H), 7.39 (s br, 3H), 7.35 (d, J = 8.1 Hz, 1H), 7.10 (t, J = 55.8 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H) ppm.
41	2.06	503.2	(DMSO-d_6) δ 10.82 (s, 1H), 8.33 - 8.26 (m, 1H), 8.03 (d, J = 2.3 Hz, 1H), 7.88 - 7.76 (m, 2H), 7.61 - 7.49 (m, 2H), 7.43 - 7.00 (m, 8H) ppm.
42	2.04	501.1	
43	1.92	485.3	(DMSO-d_6) δ ppm10.82 (s, 1H), 8.35 - 8.25 (m, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.82 - 7.73 (m, 1H), 7.62 (dd, J = 8.2, 1.6 Hz, 1H), 7.59 - 7.50 (m, 2H),

Cmpd. No	LCMS Retention Time in minutes	(M+1)	^{1}H-NMR (400 MHz)
			7.40 (s, 2H), 7.31 - 7.10 (m, 3H), 7.06 - 6.94 (m, 1H), 3.83 (s, 3H) ppm.
44	1.94	467.2	
45	2.01	481.3	
46	2.1	495.4	
47	1.98	451.2	
48	2.0	501.2	
49	2.0	481.3	
50	1.97	497.4	
51	2.08	521.4	(DMSO-d_6) δ 10.86 (s, 1H), 8.26 (s, 1H), 7.91 (d, J = 7.9 Hz, 1H), 7.78 - 7.68 (m, 2H), 7.60 - 7.49 (m, 2H), 7.45 - 7.38 (m, 4H), 7.36 (s, 1H), 7.26 - 7.19 (m, 2H) ppm.
52	1.91	485.4	
53	2.05	495.5	(DMSO-d_6) δ 10.82 (s, 1H), 8.36 - 8.28 (m, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.83 - 7.76 (m, 1H), 7.61 - 7.49 (m, 3H), 7.39 (s, 2H), 7.17 - 7.08 (m, 2H), 7.07 - 6.93 (m, 3H), 4.65 - 4.50 (m, 1H), 1.25 (d, J = 6.0 Hz, 6H) ppm.
54	1.99	501.2	(DMSO-d_6) δ 10.68 (s, 1H), 8.37 - 8.30 (m, 1H), 7.84 - 7.79 (m, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.60 - 7.50 (m, 2H), 7.40 (s, 2H), 7.37 - 7.28 (m, 1H), 7.23 - 7.11 (m, 2H), 6.93 - 6.82 (m, 1H), 6.58 - 6.50 (m, 1H), 3.75 (s, 3H) ppm.
55	1.96	471.3	(DMSO-d_6) δ 10.75 (s, 1H), 8.32 - 8.28 (m, 1H), 7.84 - 7.74 (m, 2H), 7.59 - 7.49 (m, 2H), 7.39 (s, 2H), 7.33 - 7.25 (m, 3H), 7.25 - 7.18 (m, 2H), 6.87 - 6.79 (m, 1H) ppm.
56	2.0	505.2	(DMSO-d_6) δ 10.77 (s, 1H), 8.36 - 8.28 (m, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.80 - 7.74 (m, 1H), 7.64 (dd, J = 8.4, 2.9 Hz, 1H), 7.59 - 7.48 (m, 2H), 7.40 (s, 2H), 7.38 - 7.26 (m, 3H), 6.79 (d, J = 2.2 Hz, 1H) ppm.
57	1.19	467	
58	1.34	485	(DMSO-d_6) δ 11.03 (s, 1H), 8.29 (t, J = 1.8 Hz, 1H), 7.72 (dt, J = 7.3, 2.0 Hz, 1H), 7.67 - 7.50 (m, 4H), 7.43 (d, J = 2.5 Hz, 1H), 7.41 (s, 2H), 7.32 (dd, J = 8.6, 2.7 Hz, 1H), 7.12 - 7.04 (m, 2H), 2.15 (s, 3H) ppm.
59	1.26	469	(DMSO-d_6) δ 11.05 (s, 1H), 8.29 (t, J = 1.8 Hz, 1H), 7.72 (dt, J = 7.3, 2.0 Hz, 1H), 7.68 - 7.50 (m,

Cmpd. No	LCMS Retention Time in minutes	(M+1)	^{1}H-NMR (400 MHz)
			4H), 7.41 (s, 2H), 7.30 (td, J = 8.2, 6.5 Hz, 1H), 7.12 (d, J = 7.2 Hz, 1H), 7.10 - 7.04 (m, 1H), 6.91 (d, J = 8.2 Hz, 1H), 2.08 (s, 3H) ppm.
60	1.36	521	
61	1.20	485	
62	1.93	517.2	
63	1.89	487.3	
64	1.87	519.3	
65	1.96	517.2	
66	1.92	517.2	
67	1.85	501.1	
68	1.87	501.2	
69	1.75	505.3	
70	1.78	535.3	(DMSO-d_6) δ 10.83 (s, 1H), 8.35 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.84 - 7.77 (m, 1H), 7.62 - 7.49 (m, 3H), 7.40 (s, 2H), 7.32 (dd, J = 8.8, 5.9 Hz, 1H), 7.16 (dd, J = 10.6, 2.8 Hz, 1H), 6.88 (ddd, J = 8.4, 2.8 Hz, 1H), 6.76 (s, 1H), 3.73 (s, 3H) ppm.
71	1.84	551.3	
72	1.79	551.1	
73	1.83	471.3	(DMSO-d_6) δ 10.86 (s, 1H), 8.32 - 8.27 (m, 1H), 7.91 (d, J = 7.9 Hz, 1H), 7.81 - 7.73 (m, 1H), 7.73 - 7.65 (m, 1H), 7.61 (dd, J = 8.0, 1.6 Hz, 1H), 7.58 - 7.50 (m, 2H), 7.48 - 7.36 (m, 3H), 7.32 - 7.21 (m, 2H), 7.10 (d, J = 1.6 Hz, 1H) ppm.
74	1.53	471.1	
75	1.55	501.3	(CD_3OD) δ 8.31 (t, J = 2.0 Hz, 1H), 7.79 (ddd, J = 8.1, 2.2, 1.1 Hz, 1H), 7.68 (dt, J = 8.1, 1.3 Hz, 1H), 7.57 - 7.50 (m, 2H), 7.48 (d, J = 7.8 Hz, 1H), 7.16 (d, J = 9.0 Hz, 1H), 7.09 (d, J = 2.9 Hz, 1H), 6.93 (dd, J = 9.1, 2.4 Hz, 2H), 3.81 (s, 3H) ppm.
76	1.76	498.5	(DMSO-d_6) δ 10.67 (s, 1H), 8.31 (s, 1H), 7.91 (s, 1H), 7.86 - 7.79 (m, 1H), 7.58 - 7.51 (m, 2H), 7.40 (s, 2H), 7.21 (d, J = 8.8 Hz, 1H), 6.78 - 6.71 (m, 2H), 6.59 (dd, J = 8.9, 2.8 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H) ppm.
77	1.74	485.3	(DMSO-d_6) δ 10.70 (s, 1H), 8.33 - 8.26 (m, 1H), 7.93 (s, 1H), 7.80 (dt, J = 6.4, 2.3 Hz, 1H), 7.60 - 7.49 (m, 2H), 7.40 (s, 2H), 7.29 (dd, J = 8.8, 5.8 Hz, 1H), 7.14 (dd, J = 10.7, 2.9 Hz, 1H), 6.89 - 6.79 (m, 2H), 3.76 (s, 3H) ppm.

Cmpd. No	LCMS Retention Time in minutes	(M+1)	^{1}H-NMR (400 MHz)
78	1.70	455.5	(DMSO-d_6) δ 10.77 (s, 1H), 8.28 - 8.23 (m, 1H), 7.98 (s, 1H), 7.76 (dt, J = 6.9, 2.1 Hz, 1H), 7.59 - 7.49 (m, 2H), 7.39 (s, 2H), 7.26 (t, J = 8.7 Hz, 2H), 7.22 - 7.16 (m, 3H) ppm.
79	1.70	485.3	(DMSO-d_6) δ 10.74 (s, 1H), 8.29 - 8.23 (m, 1H), 7.96 (s, 1H), 7.77 (dt, J = 7.0, 2.2 Hz, 1H), 7.60 - 7.50 (m, 2H), 7.40 (s, 2H), 7.25 - 7.14 (m, 3H), 6.97 (dt, J = 9.4, 1.9 Hz, 1H), 3.83 (s, 3H) ppm.
80	1.82	503.1	(DMSO-d_6) δ 10.80 (s, 1H), 8.32 - 8.28 (m, 1H), 7.96 (s, 1H), 7.80 (dt, J = 6.8, 2.2 Hz, 1H), 7.59 - 7.51 (m, 2H), 7.40 (s, 2H), 7.29 (t, J = 9.2 Hz, 1H), 7.06 (dd, J = 12.6, 2.9 Hz, 1H), 7.01 (s, 1H), 6.84 (ddd, J = 9.1, 3.0, 1.3 Hz, 1H), 3.78 (s, 3H) ppm.
81	1.72	485.3	(DMSO-d_6) δ 10.80 (s, 1H), 8.32 - 8.28 (m, 1H), 7.96 (s, 1H), 7.80 (dt, J = 6.8, 2.2 Hz, 1H), 7.61 - 7.51 (m, 2H), 7.40 (s, 2H), 7.29 (t, J = 9.2 Hz, 1H), 7.06 (dd, J = 12.6, 2.9 Hz, 1H), 7.01 (s, 1H), 6.84 (ddd, J = 9.1, 3.0, 1.3 Hz, 1H), 3.78 (s, 3H) ppm.
82	1.8	501.3	(DMSO-d_6) δ 10.77 (s, 1H), 8.33 - 8.28 (m, 1H), 7.98 (s, 1H), 7.79 (dt, J = 6.8, 2.2 Hz, 1H), 7.59 - 7.51 (m, 2H), 7.40 (s, 2H), 7.32 (d, J = 9.0 Hz, 1H), 7.20 (d, J = 3.0 Hz, 1H), 7.02 (dd, J = 9.0, 3.0 Hz, 1H), 6.89 (s, 1H), 3.79 (s, 3H) ppm.
83	1.78	469.3	(DMSO-d_6) δ 10.78 (s, 1H), 8.31 - 8.27 (m, 1H), 7.97 (s, 1H), 7.77 (dt, J = 7.0, 2.1 Hz, 1H), 7.62 - 7.50 (m, 2H), 7.40 (s, 2H), 7.21 (dd, J = 9.4, 2.9 Hz, 1H), 7.15 - 7.04 (m, 2H), 6.95 (s, 1H), 2.17 (s, 3H) ppm.
84	1.65	463.3	(DMSO-d_6) δ 10.55 (s, 1H), 8.32 (s, 1H), 7.82 (d, J = 3.5 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.62 - 7.51 (m, 2H), 7.39 (s, 2H), 7.30 - 7.19 (m, 2H), 6.76 (d, J = 2.7 Hz, 1H), 6.60 (dd, J = 8.8, 2.7 Hz, 1H), 6.56 (d, J = 1.8 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H) ppm.
85	1.71	467.1	
86	1.67	467.1	(DMSO-d_6) δ 10.60 (s, 1H), 8.30 (s, 1H), 7.80 (s br, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.63 - 7.50 (m, 2H), 7.39 (s, 2H), 7.32 - 7.20 (m, 3H), 7.13 - 7.05 (m, 1H), 6.72 (d, J = 1.8 Hz, 1H), 3.77 (s, 3H) ppm.
87	1.76	461.3	
88	1.77	523.2	(DMSO-d_6) δ 11.16 (s, 1H), 8.25 (t, J = 1.8 Hz, 1H), 7.99 (s, 1H), 7.72 (dt, J = 7.4, 1.9 Hz, 1H),

Cmpd. No	LCMS Retention Time in minutes	(M+1)	^{1}H-NMR (400 MHz)
			7.63 - 7.52 (m, 2H), 7.48 (s, 1H), 7.43 (s, 2H), 7.37 - 7.22 (m, 4H) ppm.
89	1.87	553.2	
90	1.83	553.2	
91	1.87	553.23	
92	1.85	553.23	
93	1.93	537.2	
94	1.57	455.3	(DMSO-d_6) δ 11.06 (s, 1H), 8.30 (s, 1H), 7.77 - 7.71 (m, 1H), 7.59 - 7.52 (m, 3H), 7.41 (s, 2H), 7.29 (dd, J = 8.7 Hz, 2H), 7.25 - 7.19 (m, 2H), 6.90 (d, J = 1.8 Hz, 1H) ppm.
95	1.58	485.5	(DMSO-d_6) δ 11.02 (s, 1H), 8.34 (s, 1H), 7.81 - 7.74 (m, 1H), 7.61 - 7.53 (m, 2H), 7.48 (d, J = 1.8 Hz, 1H), 7.41 (s, 2H), 7.21 (dd, J = 8.8, 5.8 Hz, 1H), 7.15 (dd, J = 10.6, 2.9 Hz, 1H), 6.89 - 6.81 (m, 1H), 6.60 (d, J = 1.8 Hz, 1H), 3.78 (s, 3H) ppm.
96	1.64	469.3	
97	1.73	521.3	
98	1.68	501.3	
99	1.58	485.5	
100	1.5	525.2	

EXAMPLE 42

ASSAYS FOR DETECTING AND MEASURING Na_V INHIBITION PROPERTIES OF COMPOUNDS

E-VIPR optical membrane potential assay method with electrical stimulation

[00290] Sodium channels are voltage-dependent proteins that can be activated by inducing membrane voltage changes by applying electric fields. The electrical stimulation instrument and methods of use are described in Ion Channel Assay Methods PCT/US01/21652, herein incorporated by reference and are referred to as E-VIPR. The instrument comprises a microtiter plate handler, an optical system for exciting the coumarin dye while simultaneously recording the coumarin and oxonol emissions, a waveform generator, a current- or voltage-controlled amplifier, and a device for inserting electrodes in well. Under integrated computer control, this instrument passes user-programmed electrical

stimulus protocols to cells within the wells of the microtiter plate.

[00291] 24 hours before the assay on E-VIPR, HEK cells expressing human Nav1.8 were seeded in 384-well poly-lysine coated plates at 15,000-20,000 cells per well. HEK cells were grown in media (exact composition is specific to each cell type and NaV subtype) supplemented with 10% FBS (Fetal Bovine Serum, qualified; GibcoBRL #16140-071) and 1% Pen-Strep (Penicillin-Streptomycin; GibcoBRL #15140-122). Cells were grown in vented cap flasks, in 90% humidity and 5% CO_2.

Reagents and Solutions:

[00292] 100 mg/mL Pluronic F-127 (Sigma #P2443), in dry DMSO

[00293] Compound Plates: 384-well round bottom plate, e.g. Corning 384-well Polypropylene Round Bottom #3656

[00294] Cell Plates: 384-well tissue culture treated plate, e.g. Greiner #781091-1B

[00295] 10 mM DiSBAC$_6$(3) (Aurora #00-100-010) in dry DMSO

[00296] 10 mM CC2-DMPE (Aurora #00-100-008) in dry DMSO

[00297] 200 mM ABSC1 in H_20

[00298] Bath1 buffer: Glucose 10mM (1.8g/L), Magnesium Chloride (Anhydrous), 1mM (0.095g/L), Calcium Chloride, 2mM (0.222g/L), HEPES 10mM (2.38g/L), Potassium Chloride, 4.5mM (0.335g/L), Sodium Chloride 160mM (9.35g/L).

[00299] Hexyl Dye Solution: Bath1 Buffer + 0.5% β-cyclodextrin (make this prior to use, Sigma #C4767), 8 μM CC2-DMPE + 2.5 μM DiSBAC$_6$(3). To make the solution Added volume of 10% Pluronic F127 stock equal to volumes of CC2-DMPE + DiSBAC$_6$(3). The order of preparation was first mix Pluronic and CC2-DMPE, then added DiSBAC$_6$(3) while vortexing, then added Bath1 + β-Cyclodextrin.

Assay Protocol:

[00300] 1) Pre-spotted compounds (in neat DMSO) into compound plates. Vehicle control (neat DMSO), the positive control (20mM DMSO stock tetracaine, 125 μM

final in assay) and test compounds were added to each well at 160x desired final concentration in neat DMSO. Final compound plate volume was 80 µL (80-fold intermediate dilution from 1 µL DMSO spot; 160-fold final dilution after transfer to cell plate). Final DMSO concentration for all wells in assay was 0.625%.

[00301] 2) Prepared Hexyl Dye Solution.

[00302] 3) Prepared cell plates. On the day of the assay, medium was aspirated and cells were washed three times with 100 µL of Bath1 Solution, maintaining 25 µL residual volume in each well.

[00303] 4) Dispensed 25 µL per well of Hexyl Dye Solution into cell plates. Incubated for 20-35 minutes at room temp or ambient conditions.

[00304] 5) Dispensed 80 µL per well of Bath1 into compound plates. Acid Yellow-17 (1 mM) was added and Potassium Chloride was altered from 4.5 to 20 mM depending on the NaV subtype and assay sensitivity.

[00305] 6) Washed cell plates three times with 100 µL per well of Bath1, leaving 25 µL of residual volume. Then transfered 25uL per well from Compound Plates to Cell Plates. Incubated for 20-35 minutes at room temp/ambient condition.

[00306] 7) Read Plate on E-VIPR. Used the current-controlled amplifier to deliver stimulation wave pulses for 10 seconds and a scan rate of 200Hz. A pre-stimulus recording was performed for 0.5 seconds to obtain the un-stimulated intensities baseline. The stimulatory waveform was followed by 0.5 seconds of post-stimulation recording to examine the relaxation to the resting state.

Data Analysis

[00307] Data was analyzed and reported as normalized ratios of emission intensities measured in the 460 nm and 580 nm channels. The response as a function of time was reported as the ratios obtained using the following formula::

$$R(t) = \frac{(\text{intensity}_{460\ nm} - \text{background}_{460\ nm})}{\text{---------}}$$

(intensity $_{580\ nm}$ - background $_{580\ nm}$)

[00308] The data was further reduced by calculating the initial (R_i) and final (R_f) ratios. These were the average ratio values during part or all of the pre-stimulation period, and during sample points during the stimulation period. The response to the stimulus $R = R_f/R_i$ was then calculated and reported as a function of time.

[00309] Control responses were obtained by performing assays in the presence of a compound with the desired properties (positive control), such as tetracaine, and in the absence of pharmacological agents (negative control). Responses to the negative (*N*) and positive (*P*) controls were calculated as above. The compound antagonist activity *A* is defined as:

$$A = \frac{R - P}{N - P} * 100 .$$

where R is the ratio response of the test compound

ELECTROPHYSIOLOGY ASSAYS FOR Na_V ACTIVITY AND INHIBITION OF TEST COMPOUNDS

[00310] Patch clamp electrophysiology was used to assess the efficacy and selectivity of sodium channel blockers in dorsal root ganglion neurons. Rat neurons were isolated from the dorsal root ganglions and maintained in culture for 2 to 10 days in the presence of NGF (50 ng/ml) (culture media consisted of NeurobasalA supplemented with B27, glutamine and antibiotics). Small diameter neurons (nociceptors, 8-12 μm in diameter) were visually identified and probed with fine tip glass electrodes connected to an amplifier (Axon Instruments). The "voltage clamp" mode was used to assess the compound's IC_{50} holding the cells at – 60 mV. In addition, the "current clamp" mode was employed to test the efficacy of the compounds in blocking action potential generation in response to current injections. The results of these experiments contributed to the definition of the efficacy profile of the compounds.

[00311] The exemplified compounds in Table 1 herein are active against Nav1.8 sodium channels as measured using the assays described herein and as presented in Table 3 below.

[00312] **Table 3.** Nav1.8 IC_{50} activity

Cmpd. No	Nav1.8 IC_{50} (uM)
1	0.014
2	0.022
3	0.016
4	0.027
5	0.021
6	0.013
7	0.012
8	0.01
9	0.028
10	0.02
11	0.024
12	0.009
13	0.002
14	0.005
15	0.013
16	0.007
17	0.005
18	0.007
19	0.016
20	0.004
21	0.023
22	0.028
23	0.014
24	0.03
25	0.004
26	0.004
27	0.006
28	0.016
29	0.005
30	0.009
31	0.006
32	0.008
33	0.005
34	0.014
35	0.005
36	0.004
37	0.006
38	0.014
39	0.01
40	0.007
41	0.022

Cmpd. No	Nav1.8 IC_{50} (uM)
42	0.01
43	0.021
44	0.02
45	0.021
46	0.014
47	0.014
48	0.01
49	0.012
50	0.008
51	0.014
52	0.011
53	0.026
54	0.005
55	0.009
56	0.004
57	0.027
58	0.006
59	0.014
60	0.009
61	0.028
62	0.016
63	0.027
64	0.022
65	0.022
66	0.007
67	0.026
68	0.009
69	0.026
70	0.013
71	0.028
72	0.02
73	0.026
74	0.015
75	0.005
76	0.003
77	0.001
78	0.008
79	0.004
80	0.004
81	0.008
82	0.006

Cmpd. No	Nav1.8 IC_{50} (uM)
83	0.005
84	0.013
85	0.015
86	0.015
87	0.029
88	0.007
89	0.001
90	0.007
91	0.007

Cmpd. No	Nav1.8 IC_{50} (uM)
92	0.016
93	0.002
94	0.005
95	0.0009
96	0.001
97	0.004
98	0.0008
99	0.005
100	0.018

EXAMPLE 43

[00313] IonWorks assays. This assay was performed to determine the activity for the compounds of the present invention against non $Na_V1.8$ channels. Sodium currents were recorded using the automated patch clamp system, IonWorks (Molecular Devices Corporation, Inc.). Cells expressing Na_V subtypes were harvested from tissue culture and placed in suspension at 0.5-4 million cells per mL Bath1. The IonWorks instrument measured changes in sodium currents in response to applied voltage clamp similarly to the traditional patch clamp assay, except in a 384-well format. Using the IonWorks, dose-response relationships were determined in voltage clamp mode by depolarizing the cell from the experiment specific holding potential to a test potential of about 0 mV before and following addition of the test compound. The influence of the compound on currents were measured at the test potential.

EXAMPLE 44

[00314] Human Liver Microsome Assay Protocol: Liver microsomal stability data were generated as follows. Substrates were incubated at 37 °C and shaken for 30 minutes in a phosphate buffered solution with human liver microsomes and the cofactor NADPH. A time zero control was similarly prepared, however with NADPH excluded. The final incubation concentrations were 1 uM substrate (0.2% DMSO), 0.5 mg/mL liver microsome, 2 mM NADPH, and 0.1 M phosphate. Reactions were quenched and proteins precipitated with the addition of 2 volume equivalents of ice cold acetonitrile containing an internal standard.

Following a centrifugation step, aliquots from the quenched incubations were further diluted with 4 volume equivalents of a 50% aqueous methanol solution and then subjected to LC/MS/MS analysis for quantitation of parent substrate. Microsome stability values were calculated as the percent of substrate remaining after 30 minutes referenced against the time zero control.

[00315] **Table 4.** Human liver microsome (HLM) data for selected compounds of the present invention is listed below. The values presented represent the percent of compound remaining after 30 minutes using the protocol described above in Example 44. Compounds with reported >100% percent unchanged after 30 minutes of incubation represent compounds that were not metabolized under the assay conditions. The numbers exceeding 100% were due to variability in the analytical quantitation of the assay. The abbreviation "ND"stands for no data.

Cmpd. No.	HLM: percent unchanged after 30 min
1	83
2	97
3	117
4	118
5	107
6	106
7	78
8	108
9	102
10	86
11	89
12	94
13	78
14	83
15	81
16	86
17	102
18	98
19	94
20	96
21	96
22	88
23	75

Cmpd. No.	HLM: percent unchanged after 30 min
24	102
25	94
26	119
27	101
28	92
29	100
30	103
31	82
32	76
33	102
34	96
35	82
36	66
37	76
38	105
39	104
40	107
41	95
42	84
43	90
44	79
45	72
46	67

Cmpd. No.	HLM: percent unchanged after 30 min
47	100
48	68
49	57
50	72
51	89
52	81
53	71
54	96
55	95
56	102
57	78
58	107
59	66
60	92
61	68
62	81
63	92
64	96
65	101
66	89
67	91
68	80
69	110
70	87
71	81
72	67
73	95

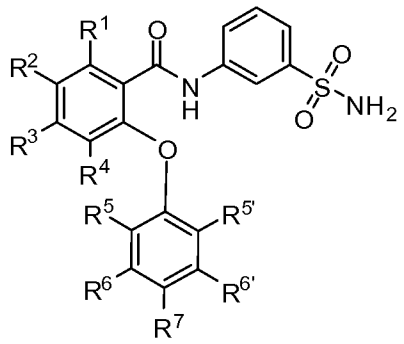
Cmpd. No.	HLM: percent unchanged after 30 min
74	102
75	62
76	58
77	95
78	104
79	91
80	108
81	88
82	77
83	93
84	82
85	ND
86	82
87	ND
88	105
89	87
90	92
91	69
92	113
93	96
94	97
95	91
96	96
97	102
98	62
99	63
100	ND

[00316] Many modifications and variations of the embodiments described herein may be made without departing from the scope, as is apparent to those skilled in the art.

The specific embodiments described herein are offered by way of example only.

We claim:

1. A compound of formula **I**



I;

or a pharmaceutically acceptable salt thereof,

wherein, independently for each occurrence:

R^1 is H, Cl, CH_3, CF_3 or cyclopropyl;

R^2 is H, F, Cl, CN, CH_3, CF_3 or CHF_2;

R^3 is H, F, Cl, CN, CF_3, OCF_3 or CF_2CF_3;

R^4 is H;

R^5 is H, F, Cl, CH_3, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$ or $OCHF_2$;

$R^{5'}$ is H, F, Cl, CH_3, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$ or $OCHF_2$;

R^6 is H, F or Cl;

$R^{6'}$ is H, F or Cl; and

R^7 is H, F, Cl, OCH_3, OCF_3, OCH_2CH_3, $OCH(CH_3)_2$ or $OCHF_2$,

provided that R^1, R^2, and R^3 are not simultaneously hydrogen; and
that R^5, $R^{5'}$, R^6, $R^{6'}$, and R^7 are not simultaneously hydrogen..

2. The compound or salt according to claim 1, wherein R^1 is H, CF_3 or Cl.

3. The compound or salt according to claim 1 or 2, wherein R^1 is H or CF_3.

4. The compound or salt according to any one of claims 1 to 3, wherein R^2 is H, CF_3 or Cl.

5. The compound or salt according to claim 4, wherein R^2 is H or CF_3.

6. The compound or salt according to any one of claims 1 to 5, wherein R^3 is H, CF_3, Cl or OCF_3.

7. The compound or salt according to claim 6, wherein R^3 is H, CF_3 or Cl.

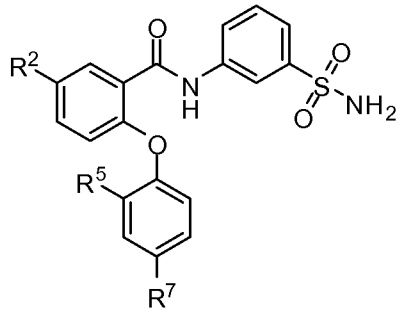
8. The compound or salt according to any one of claims 1 to 7, wherein R^5 is H.

9. The compound or salt according to any one of claims 1 to 8, wherein R^6 or $R^{6'}$ is H or F.

10. The compound or salt according to claim any one of claims 1 to 9, wherein R^7 is F, Cl, OCH_3 or OCF_3.

11. The compound or salt according to claim 10, wherein R^7 is F or OCH_3.

12. The compound or salt according claim 1, wherein the compound has formula I-D:



I-D,

wherein, independently for each occurrence:

R^2 is F, Cl, CN, CH_3, CF_3 or CHF_2;

R^5 is F, Cl, CH_3, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$ or $OCHF_2$; and

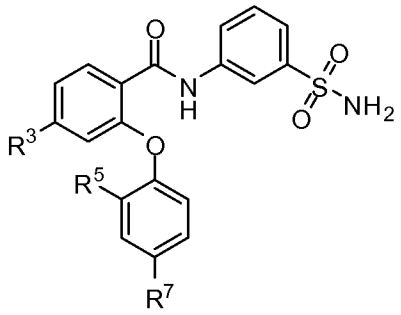
R^7 is F, Cl, OCH_3, OCF_3, OCH_2CH_3, $OCH(CH_3)_2$ or $OCHF_2$.

13. The compound or salt according to claim 12, wherein R^2 is Cl or CF_3.

14. The compound or salt according to claim 12 or 13, wherein R^5 is F, Cl, CH_3 or OCH_3.

15. The compound or salt according to any one of claims 12 to 14, wherein R^7 is F, Cl, OCH_3 or OCF_3.

16. The compound or salt according to claim 1, wherein the compound has formula I-E:



I-E,

wherein, independently for each occurrence:

R^3 is F, Cl, CN, CF_3, OCF_3 or CF_2CF_3;

R^5 is F, Cl, CH_3, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$ or $OCHF_2$; and

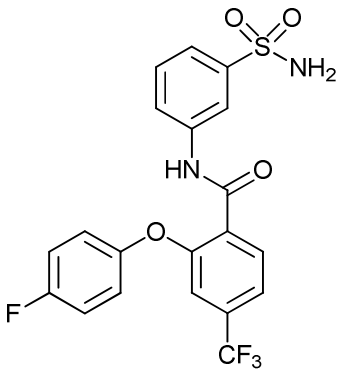
R^7 is F, Cl, OCH_3, OCF_3, OCH_2CH_3, $OCH(CH_3)_2$ or $OCHF_2$.

17. The compound or salt according to claim 16, wherein R^3 is Cl, CF_3 or OCF_3.

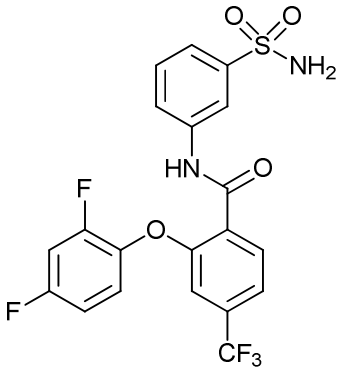
18. The compound or salt according to claim 16 or 17, wherein R^5 is F, Cl, CH_3 or OCH_3.

19. The compound or salt according to any one of claims 16 to 18, wherein R^7 is F, Cl, OCH_3 or OCF_3.

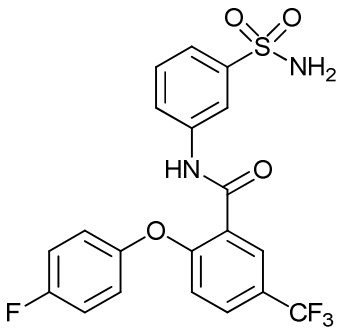
20. The compound or salt of claim 1, wherein the compound, or the pharmaceutically acceptable salt thereof, is selected from the group consisting of:



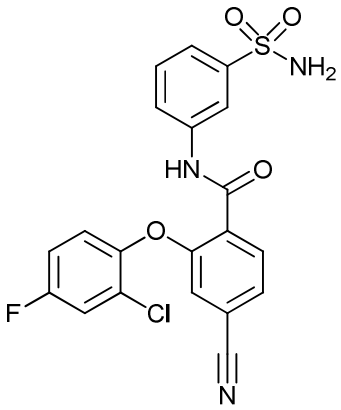
2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide;



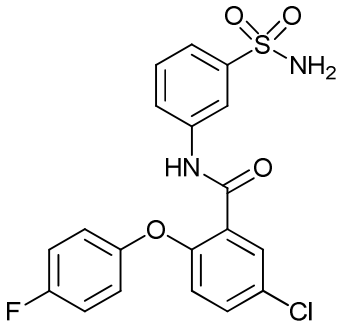
2-(2,4-difluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide;



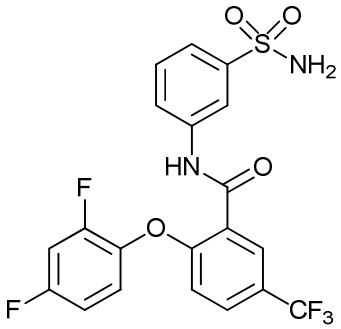
2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



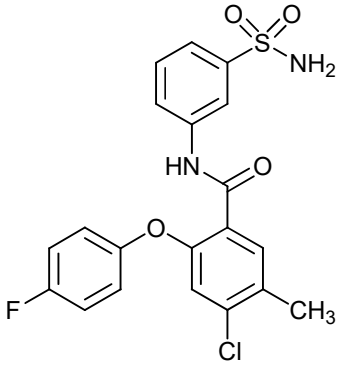
2-(2-chloro-4-fluorophenoxy)-4-cyano-N-(3-sulfamoylphenyl)benzamide;



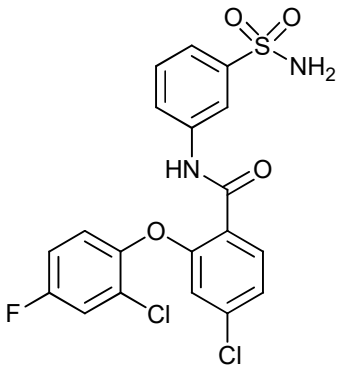
5-chloro-2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide;



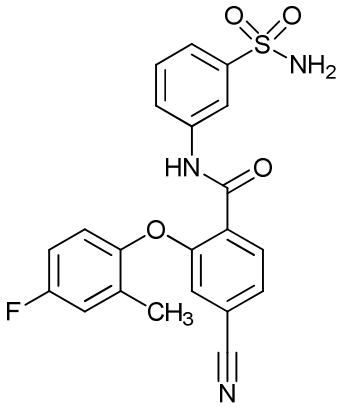
2-(2,4-difluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



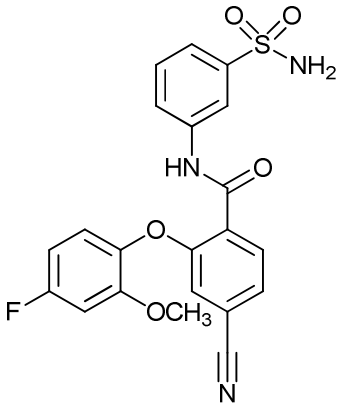
4-chloro-2-(4-fluorophenoxy)-5-methyl-N-(3-sulfamoylphenyl)benzamide;



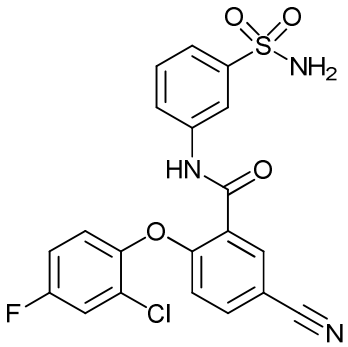
4-chloro-2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide;



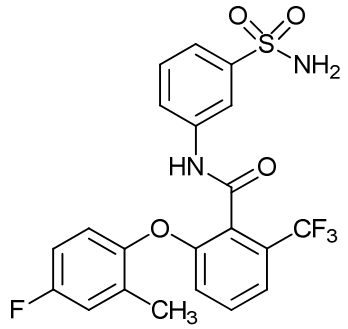
4-cyano-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide;



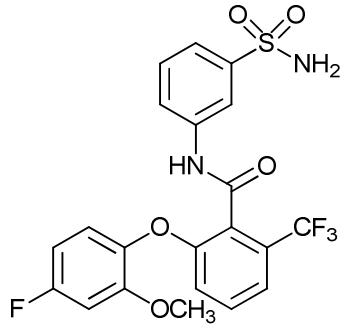
4-cyano-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide;



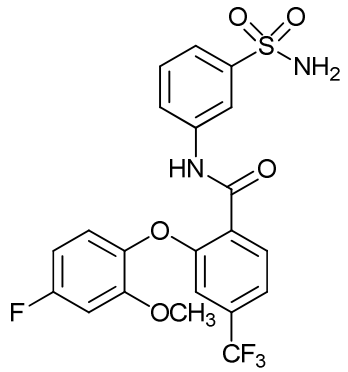
2-(2-chloro-4-fluorophenoxy)-5-cyano-N-(3-sulfamoylphenyl)benzamide;



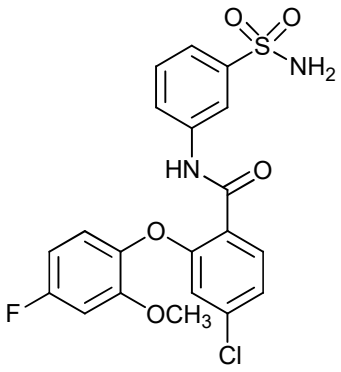
2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide;



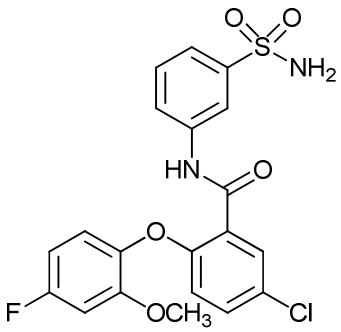
2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide;



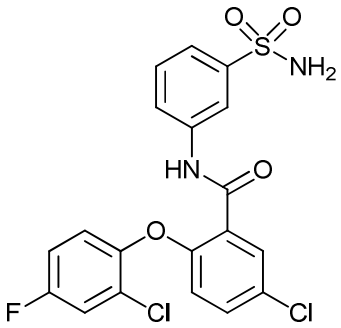
2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide;



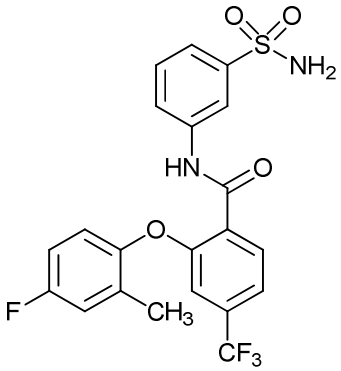
4-chloro-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide;



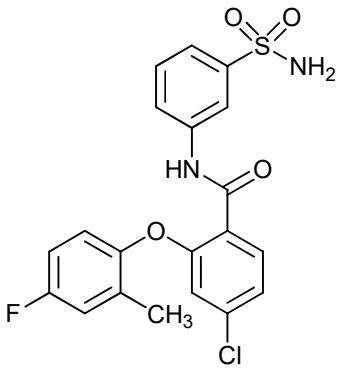
5-chloro-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide;



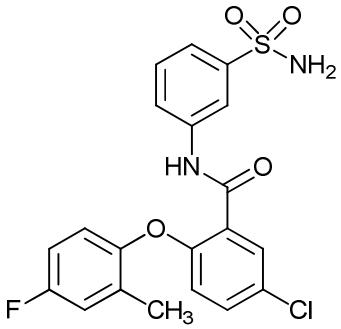
5-chloro-2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide;



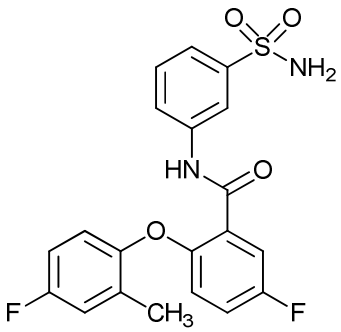
2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide;



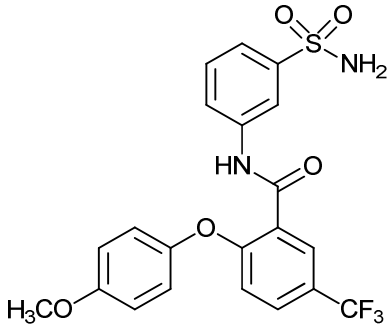
4-chloro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide;



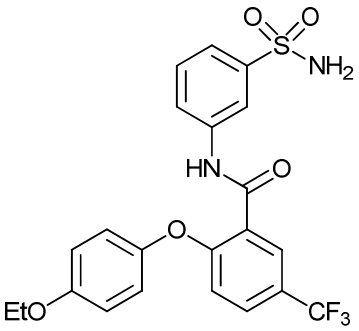
5-chloro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide;



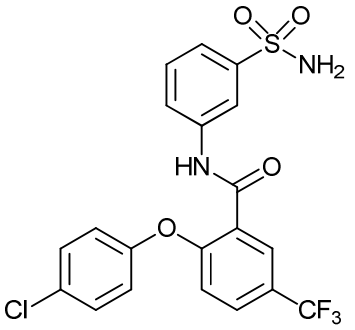
5-fluoro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide;



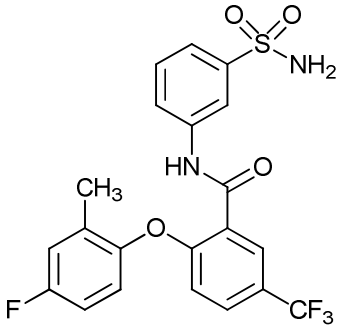
2-(4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



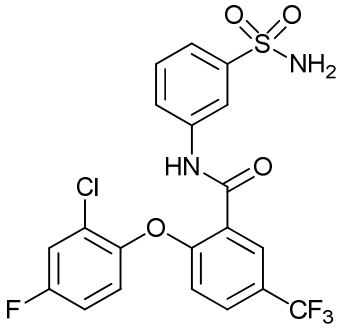
2-(4-ethoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



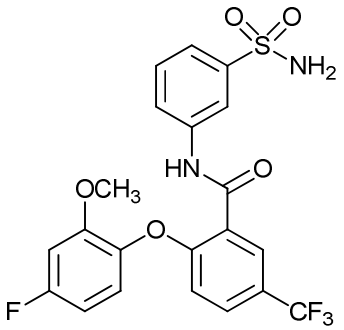
2-(4-chlorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



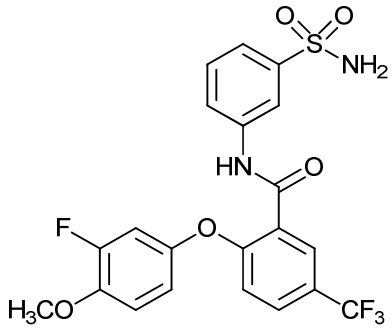
2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



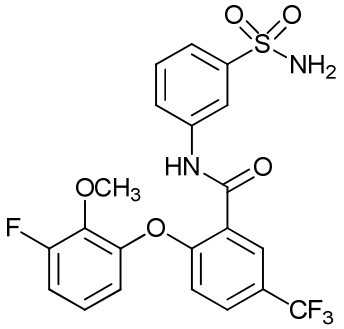
2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



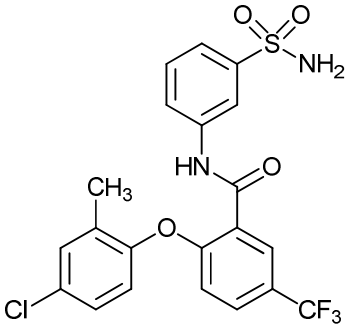
2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



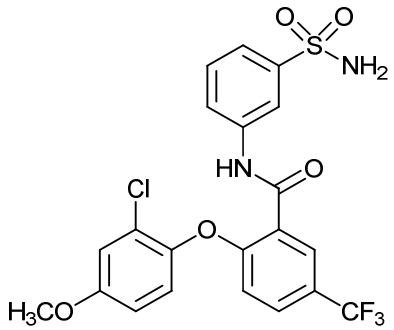
2-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



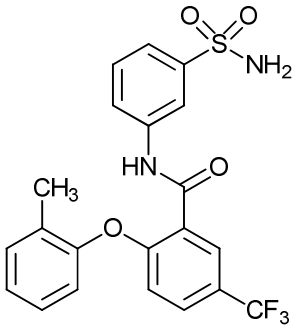
2-(3-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



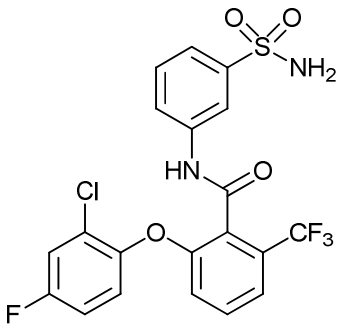
2-(4-chloro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



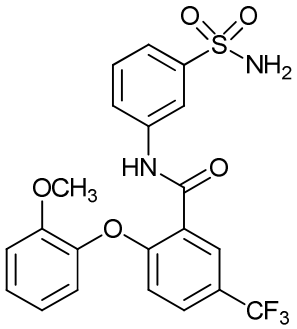
2-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



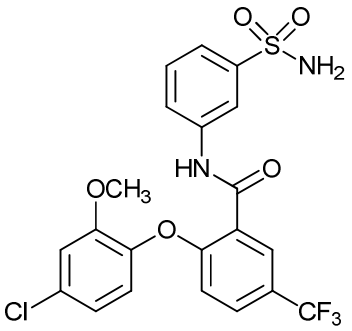
N-(3-sulfamoylphenyl)-2-(o-tolyloxy)-5-(trifluoromethyl)benzamide;



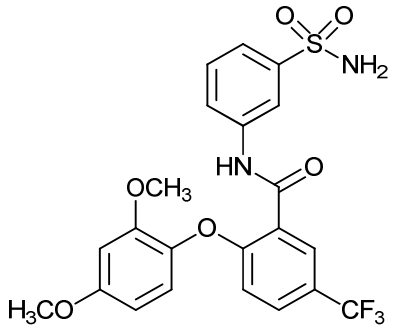
2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide;



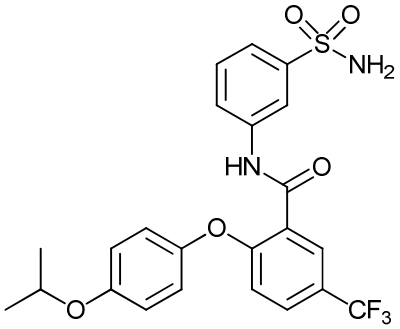
2-(2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



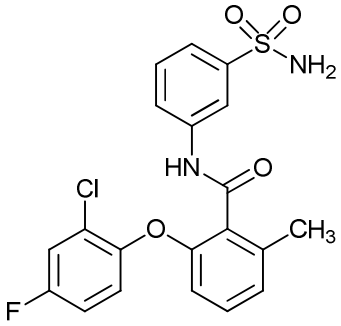
2-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



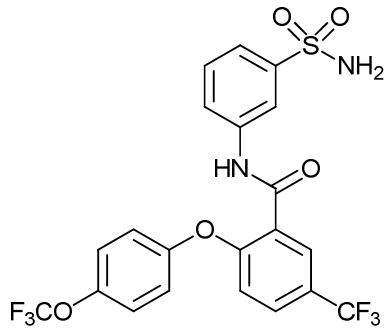
2-(2,4-dimethoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



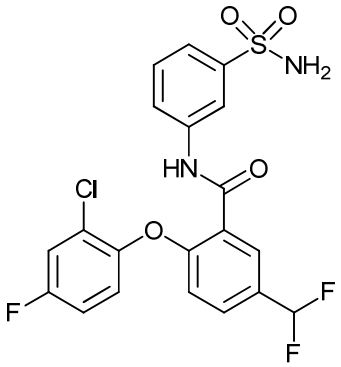
2-(4-isopropoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



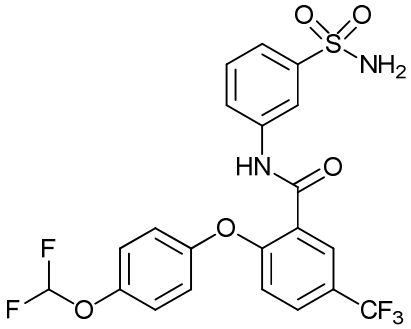
2-(2-chloro-4-fluorophenoxy)-6-methyl-N-(3-sulfamoylphenyl)benzamide;



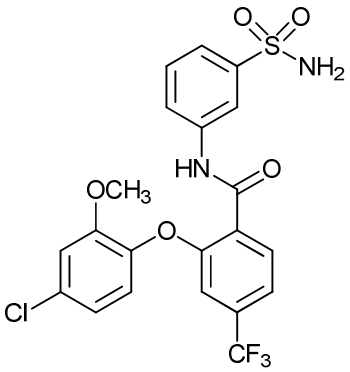
N-(3-sulfamoylphenyl)-2-(4-(trifluoromethoxy)phenoxy)-5-(trifluoromethyl)benzamide;



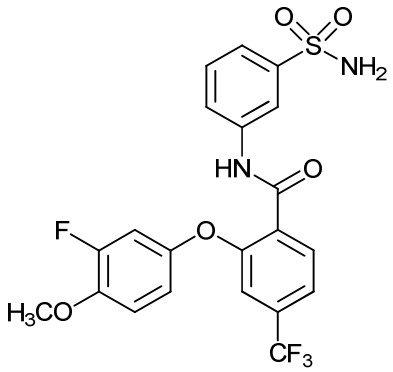
2-(2-chloro-4-fluorophenoxy)-5-(difluoromethyl)-N-(3-sulfamoylphenyl)benzamide;



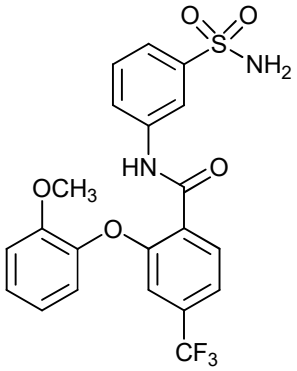
2-(4-(difluoromethoxy)phenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



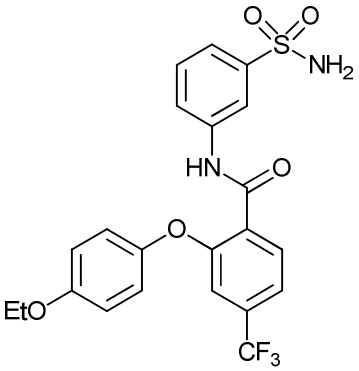
2-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide;



2-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide;



2-(2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide;



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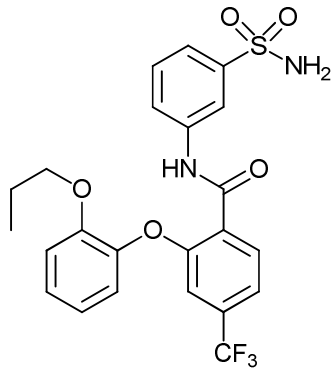

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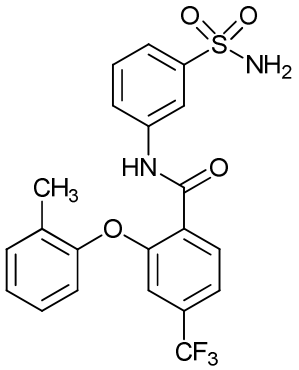

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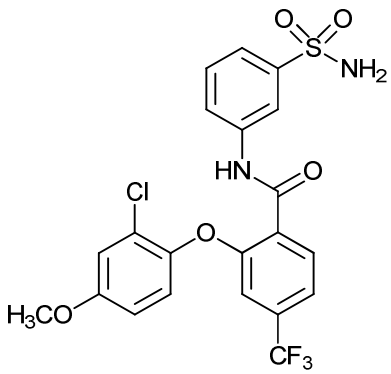

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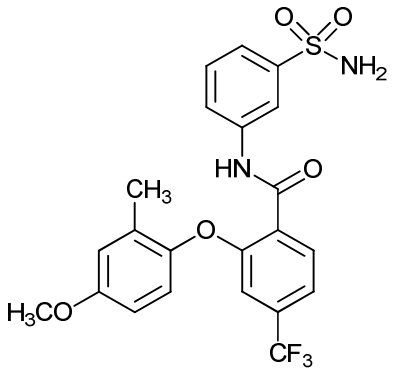

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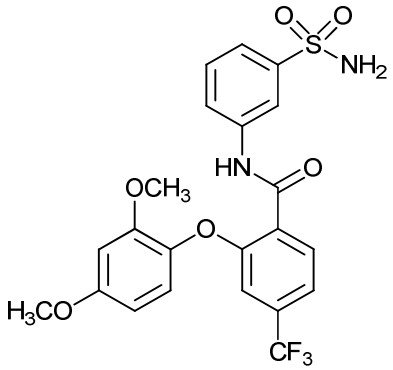

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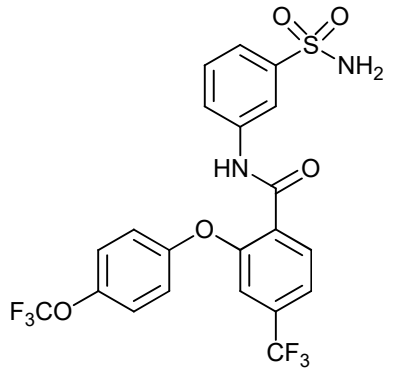

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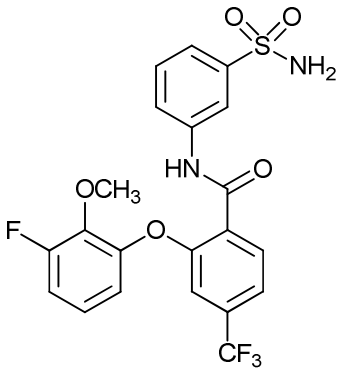

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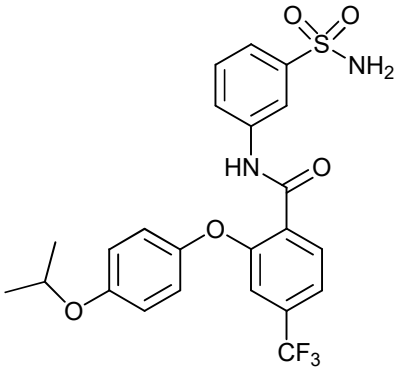

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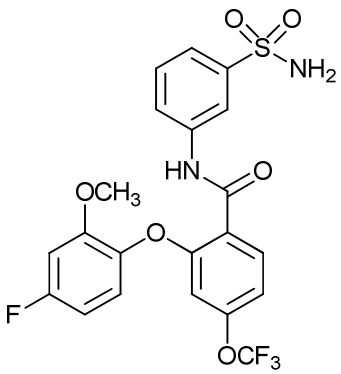

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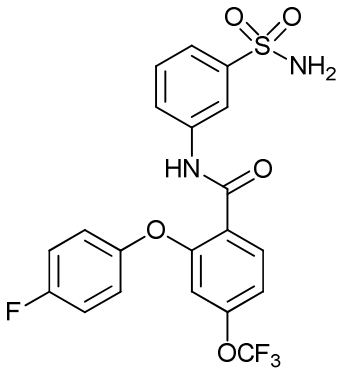

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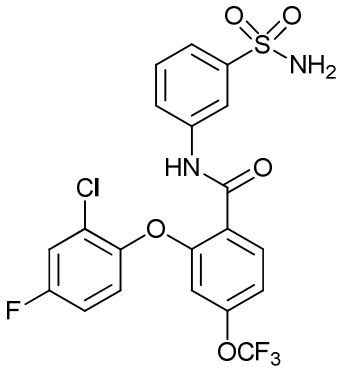

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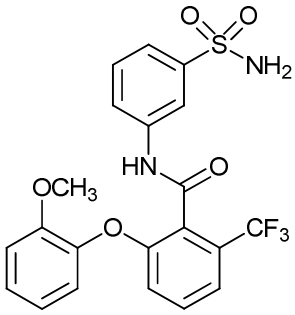

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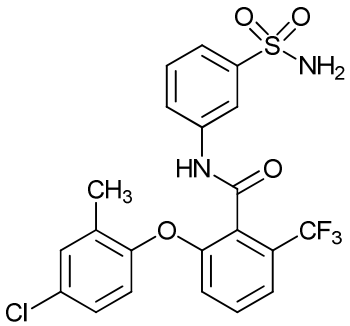

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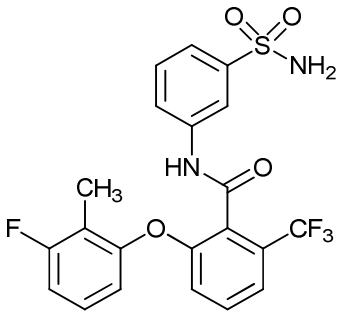

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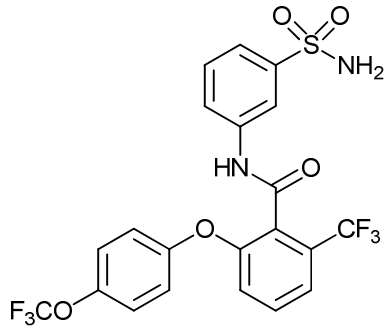

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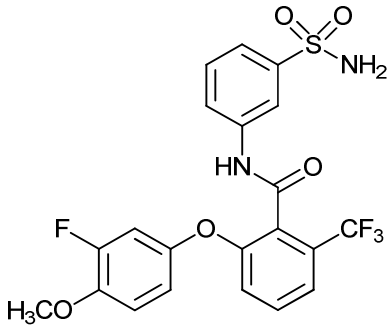

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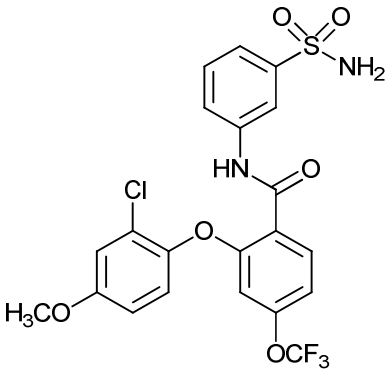

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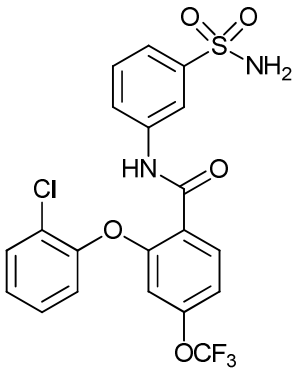
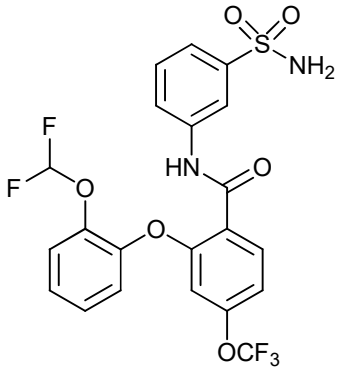
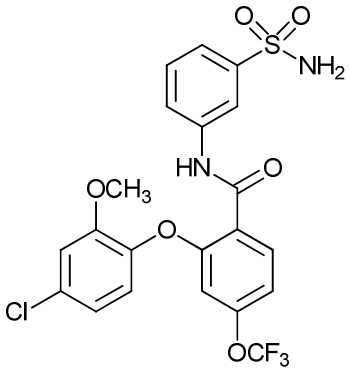


2-(2-chlorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide;



2-(2-(difluoromethoxy)phenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide;



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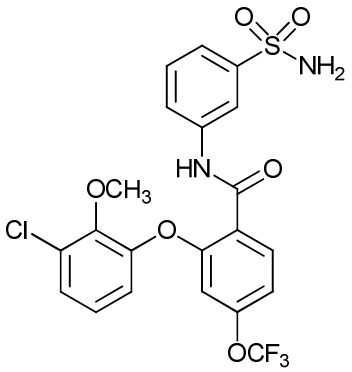

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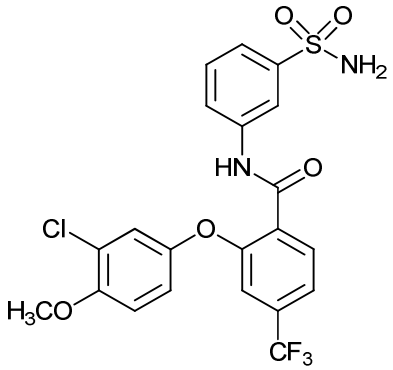

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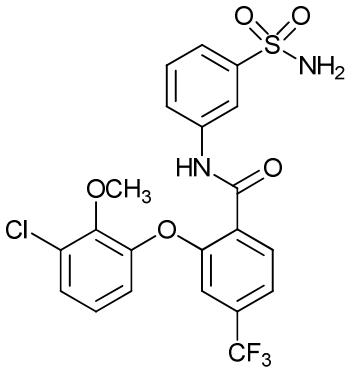

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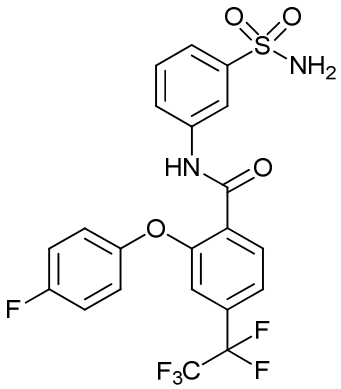

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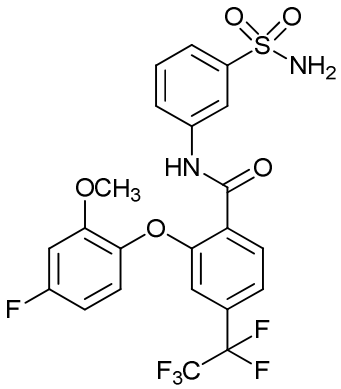

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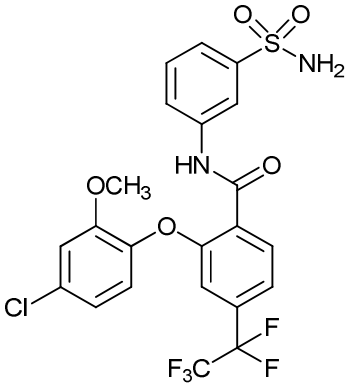

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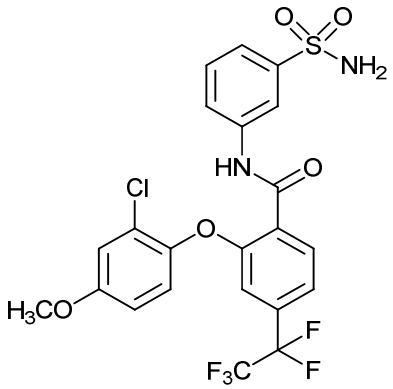

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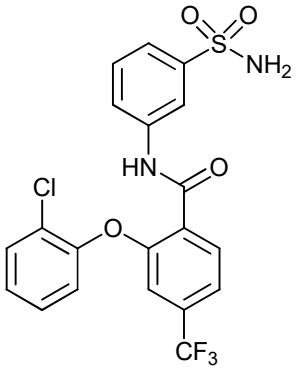

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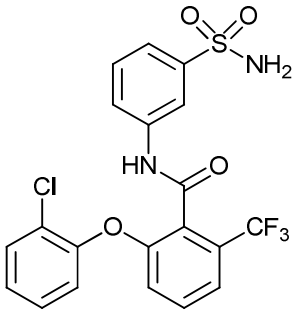

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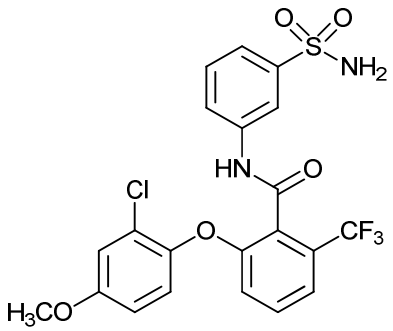

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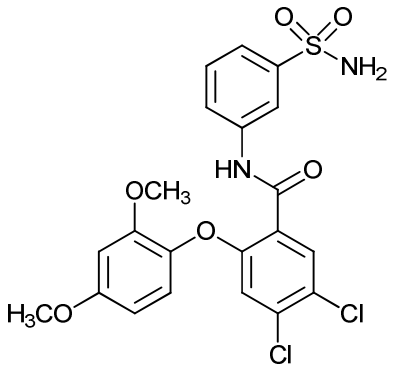

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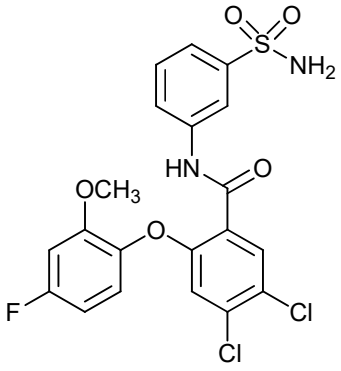

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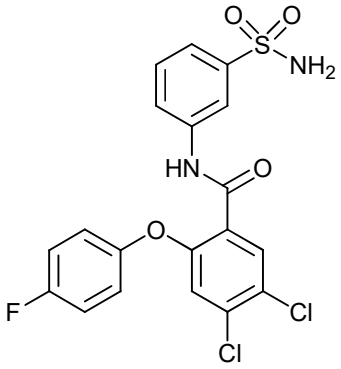

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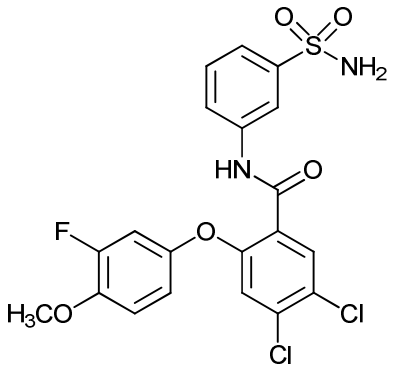

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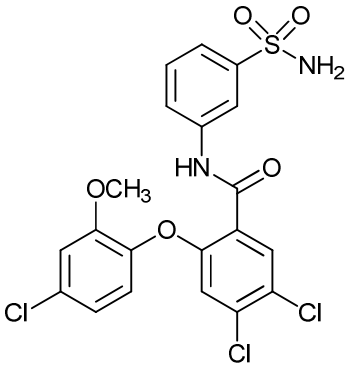

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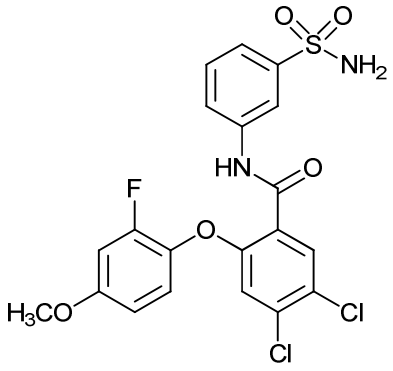

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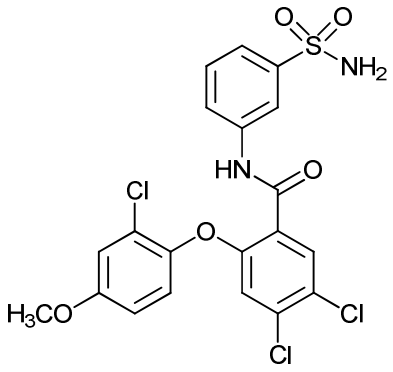
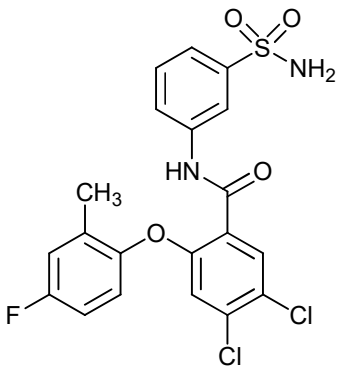
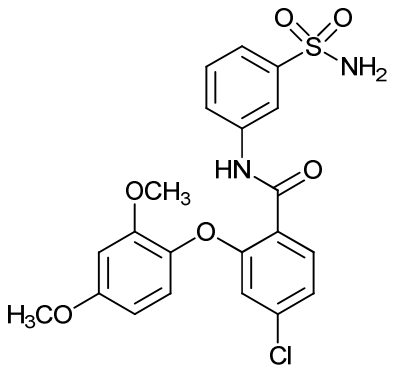


4,5-dichloro-2-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide;



4,5-dichloro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide;



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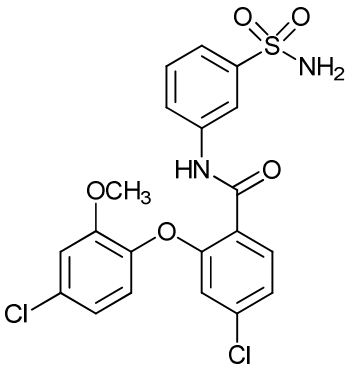

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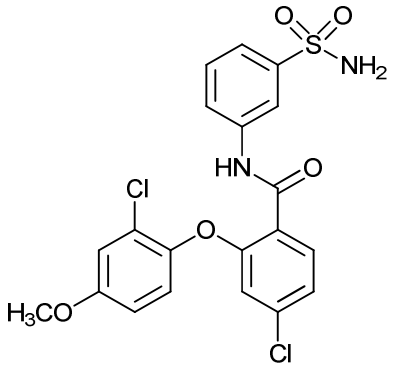

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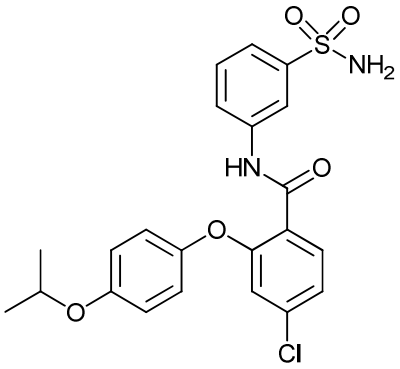
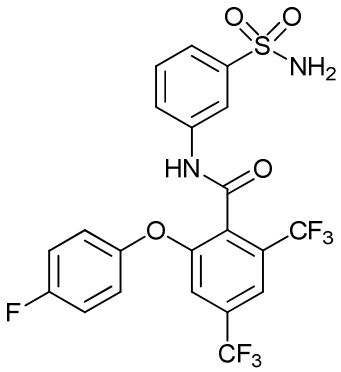


4-chloro-2-(4-isopropoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide;



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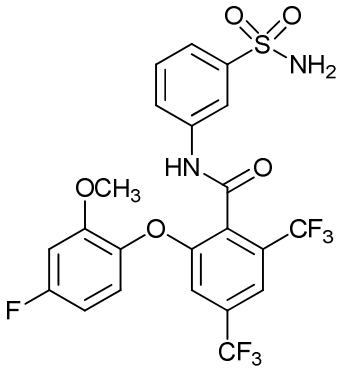

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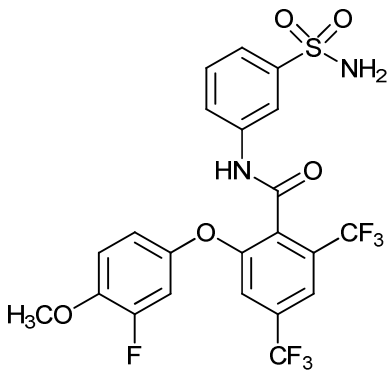

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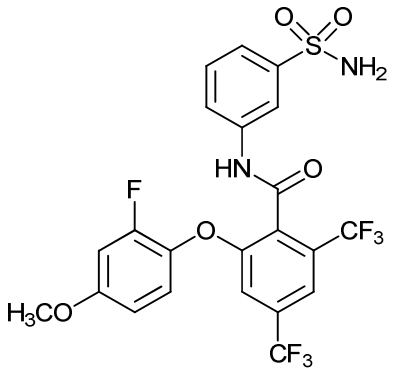

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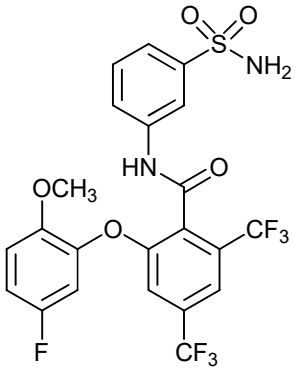
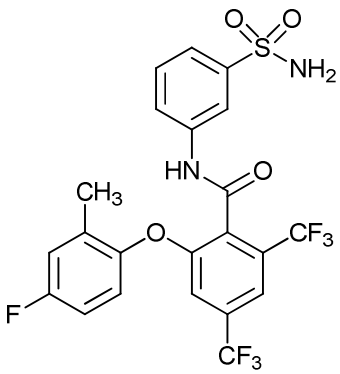
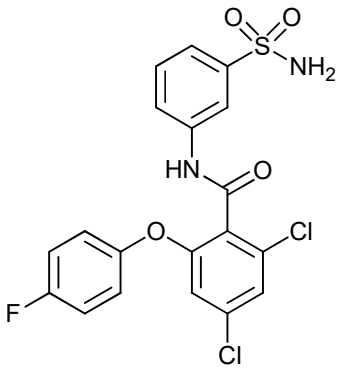


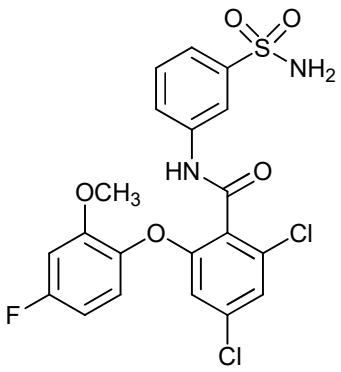
2-(5-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide;



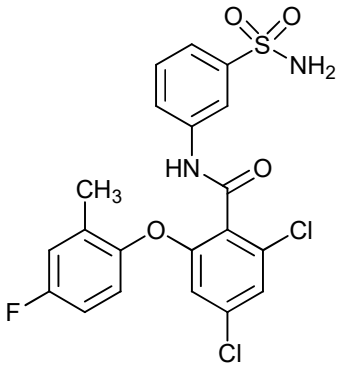
2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide;



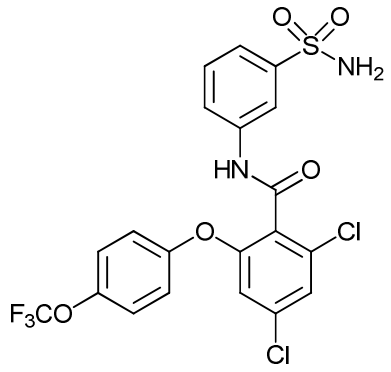
2,4-dichloro-6-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide;



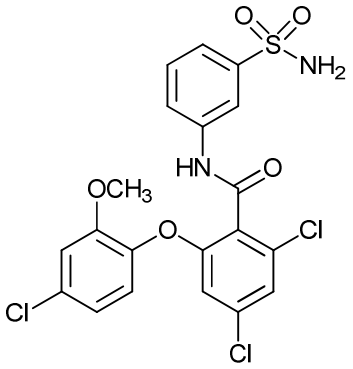
2,4-dichloro-6-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide;



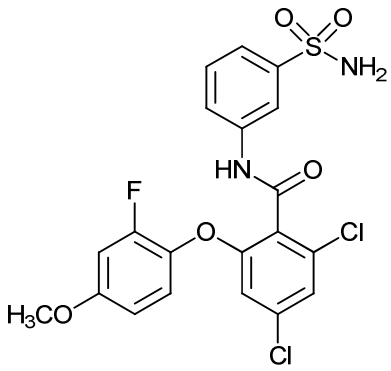
2,4-dichloro-6-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide;



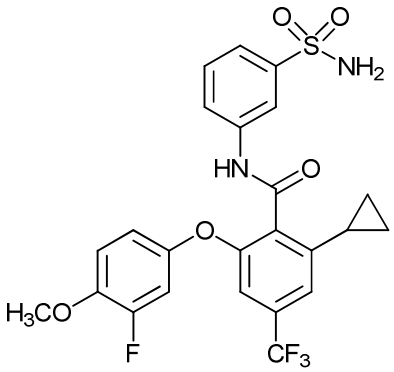
2,4-dichloro-N-(3-sulfamoylphenyl)-6-(4-(trifluoromethoxy)phenoxy)benzamide;



2,4-dichloro-6-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide;



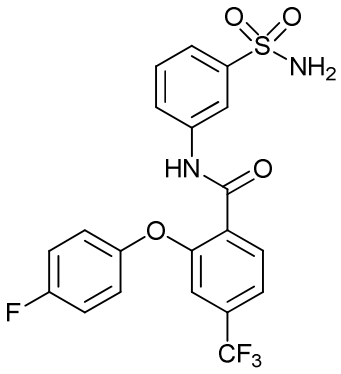
2,4-dichloro-6-(2-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide; and



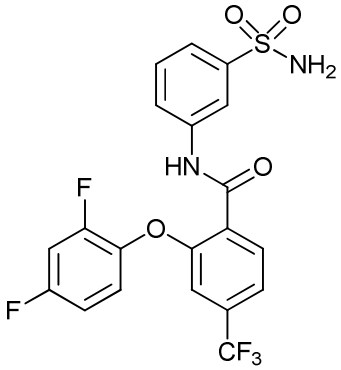
2-cyclopropyl-6-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide;

or a pharmaceutically acceptable salt thereof.

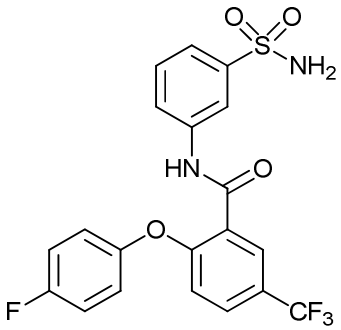
21. The compound of claim 1, wherein the compound is selected from the group consisting of:



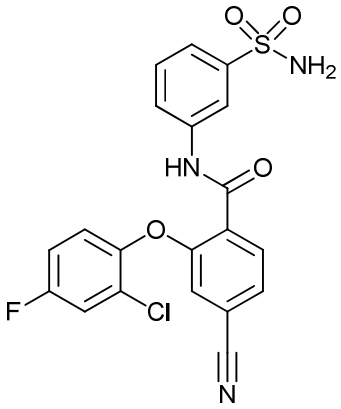
2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide;



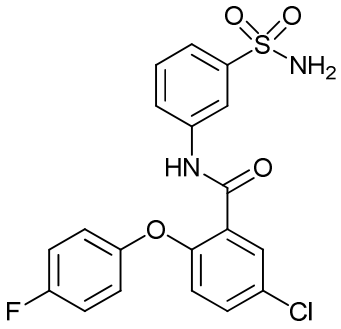
2-(2,4-difluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide;



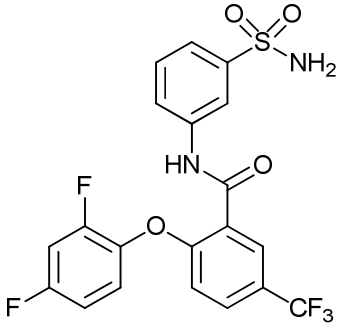
2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



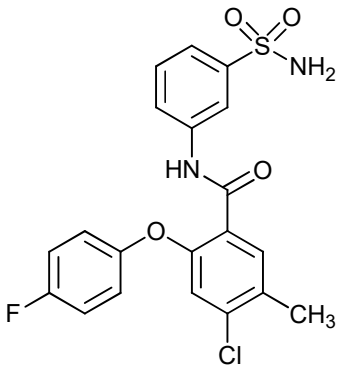
2-(2-chloro-4-fluorophenoxy)-4-cyano-N-(3-sulfamoylphenyl)benzamide;



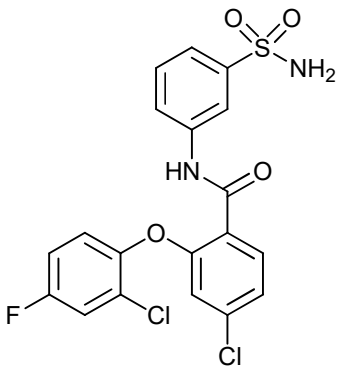
5-chloro-2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide;



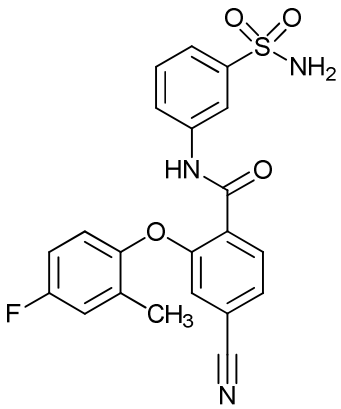
2-(2,4-difluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



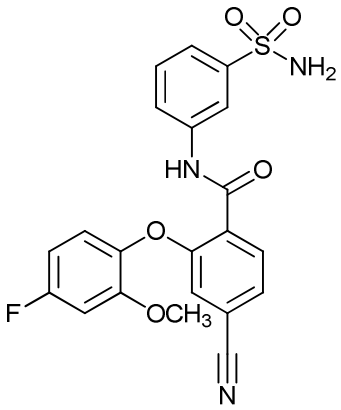
4-chloro-2-(4-fluorophenoxy)-5-methyl-N-(3-sulfamoylphenyl)benzamide;



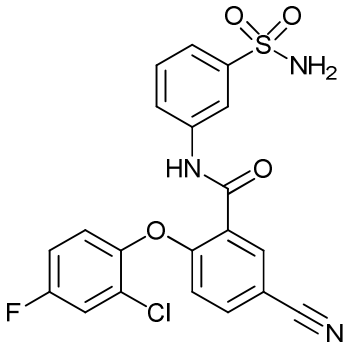
4-chloro-2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide;



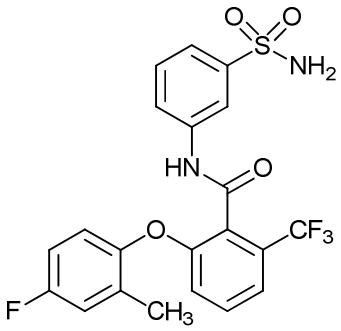
4-cyano-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide;



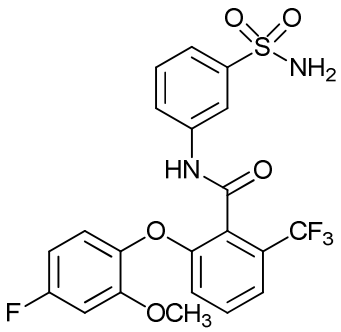
4-cyano-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide;



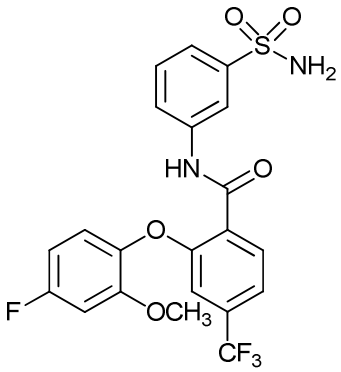
2-(2-chloro-4-fluorophenoxy)-5-cyano-N-(3-sulfamoylphenyl)benzamide;



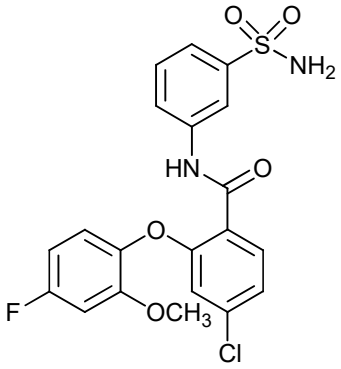
2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide;



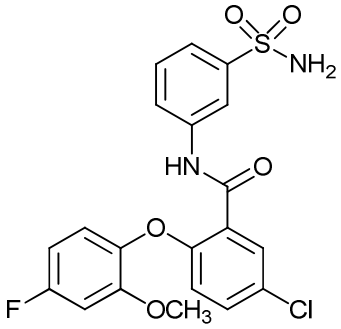
2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide;



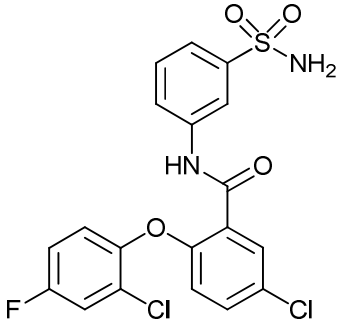
2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide;



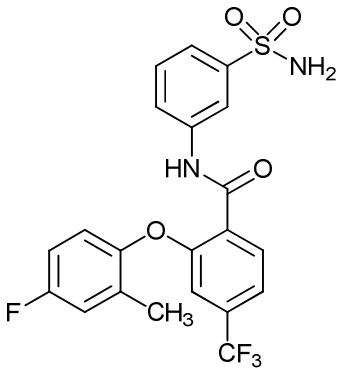
4-chloro-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide;



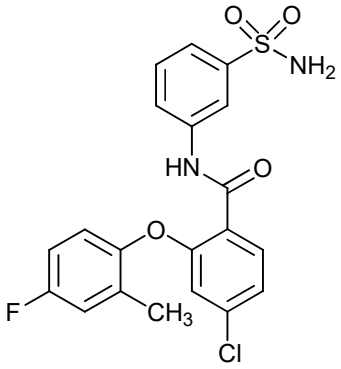
5-chloro-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide;



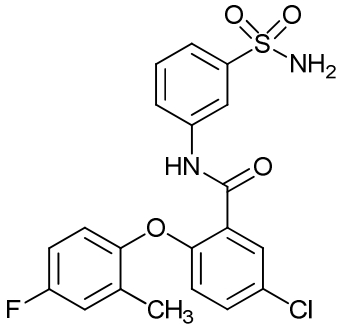
5-chloro-2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide;



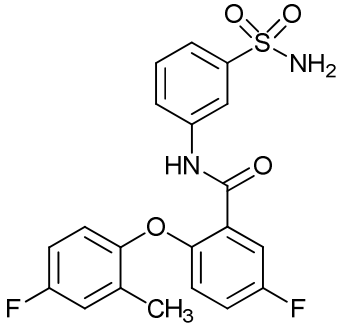
2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide;



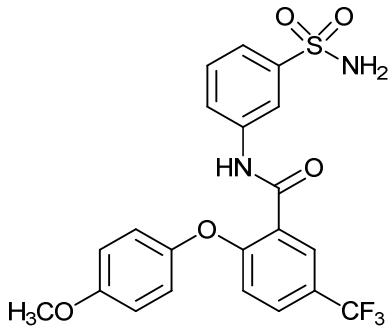
4-chloro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide;



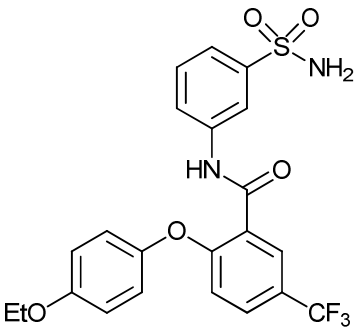
5-chloro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide;



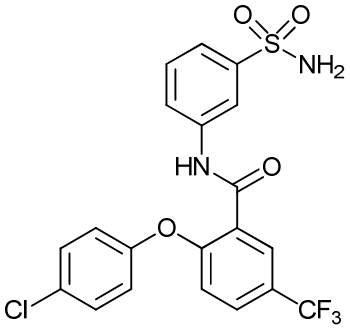
5-fluoro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide;



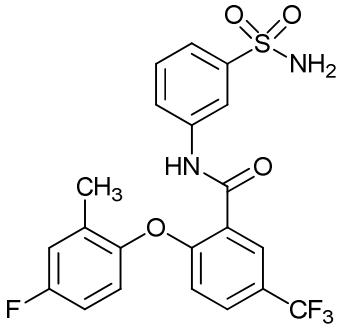
2-(4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



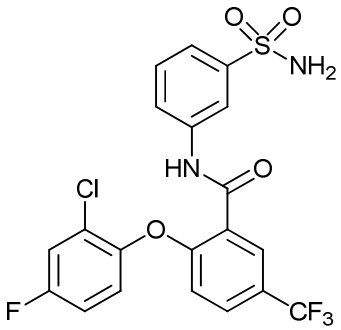
2-(4-ethoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



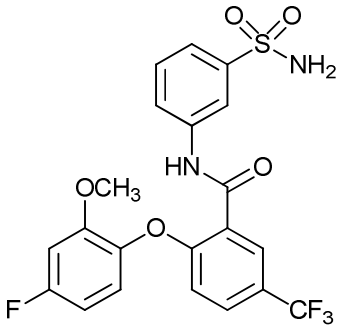
2-(4-chlorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



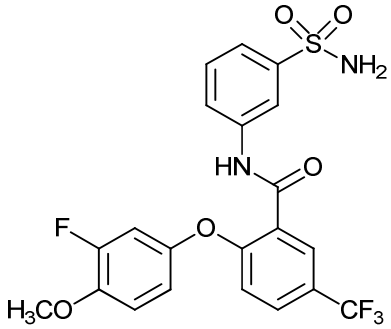
2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



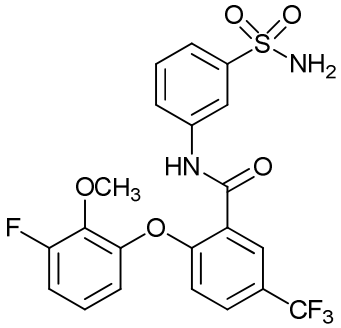
2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



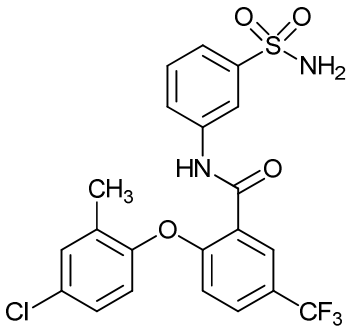
2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



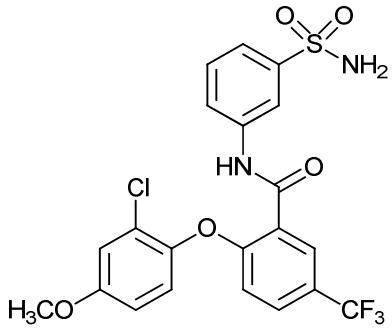
2-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



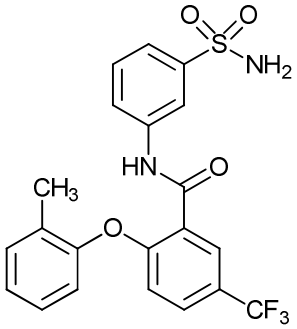
2-(3-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



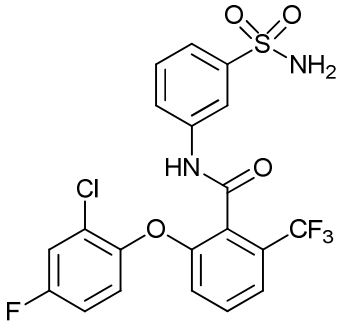
2-(4-chloro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



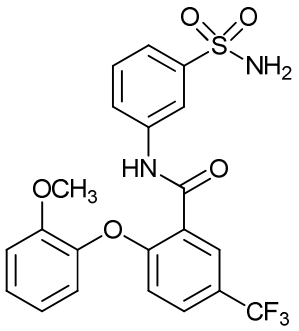
2-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



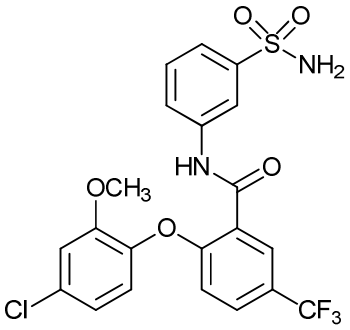
N-(3-sulfamoylphenyl)-2-(o-tolyloxy)-5-(trifluoromethyl)benzamide;



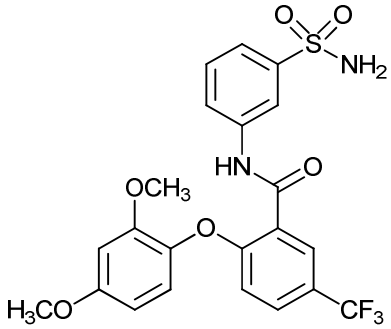
2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide;



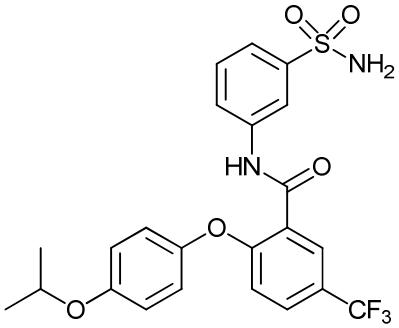
2-(2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



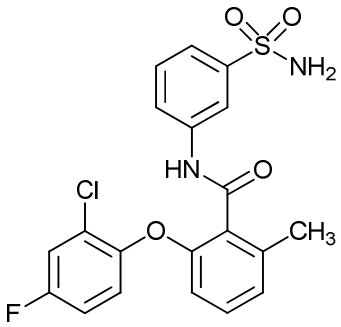
2-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



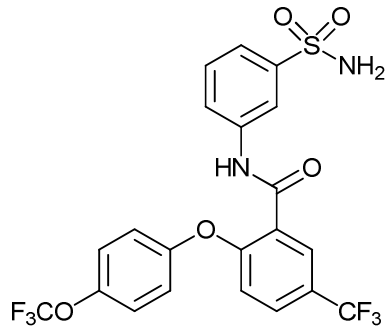
2-(2,4-dimethoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



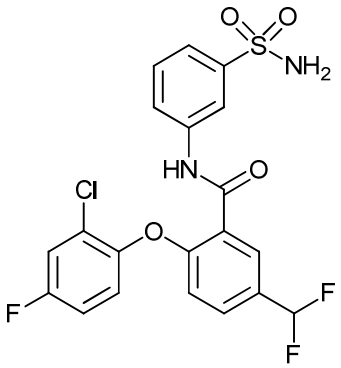
2-(4-isopropoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide;



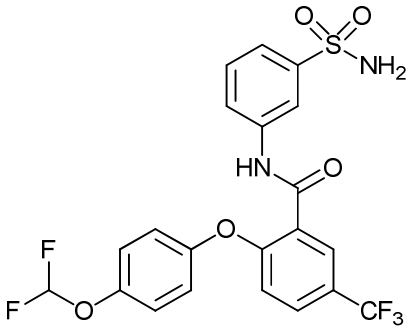
2-(2-chloro-4-fluorophenoxy)-6-methyl-N-(3-sulfamoylphenyl)benzamide;



N-(3-sulfamoylphenyl)-2-(4-(trifluoromethoxy)phenoxy)-5-(trifluoromethyl)benzamide;



2-(2-chloro-4-fluorophenoxy)-5-(difluoromethyl)-N-(3-sulfamoylphenyl)benzamide;



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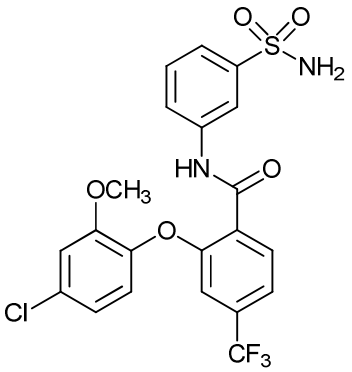

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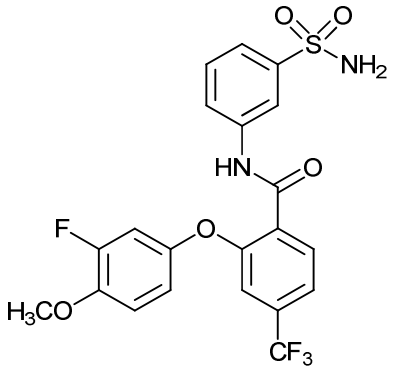

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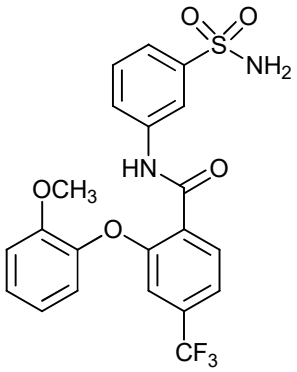

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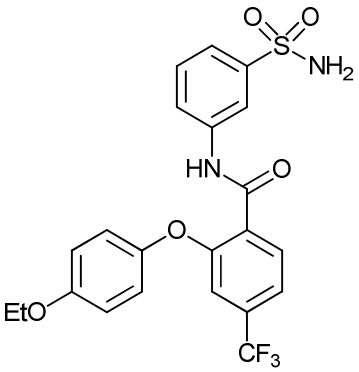

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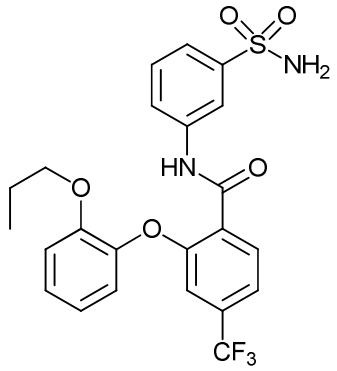
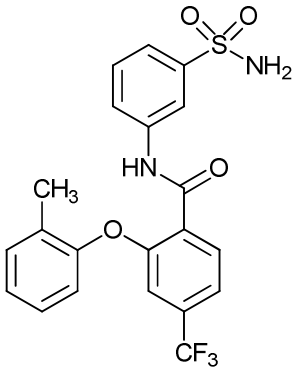
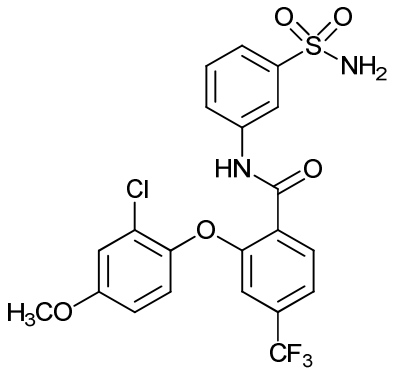


2-(2-propoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide;



N-(3-sulfamoylphenyl)-2-(o-tolyloxy)-4-(trifluoromethyl)benzamide;



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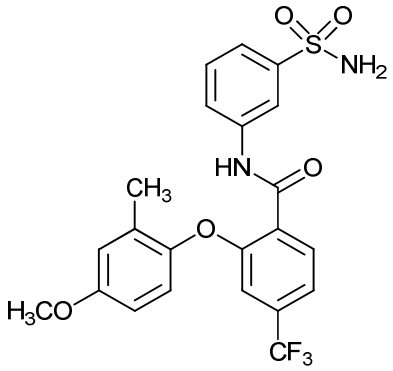

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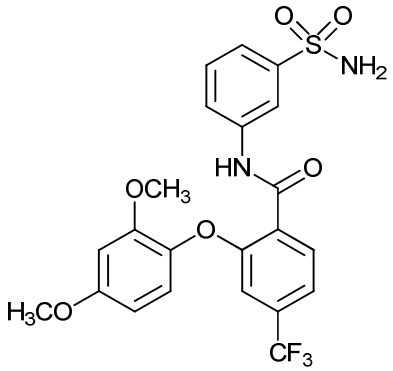

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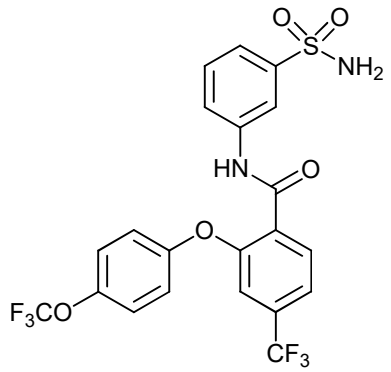

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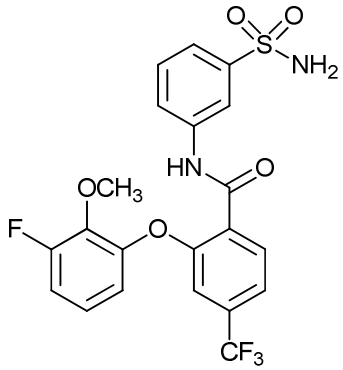

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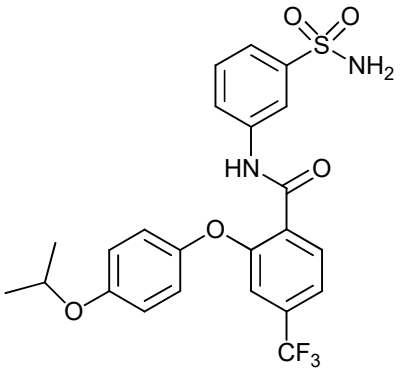
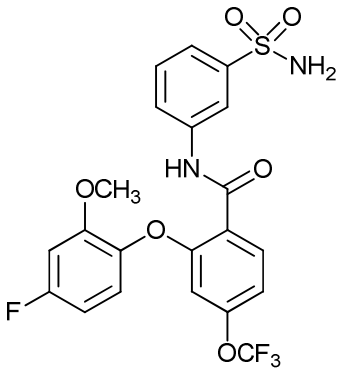


2-(4-isopropoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide;



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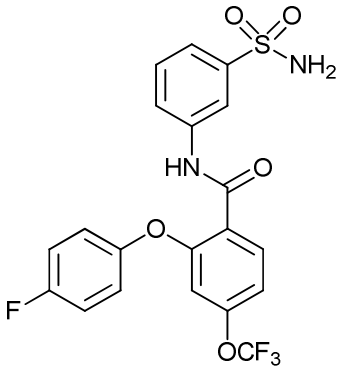
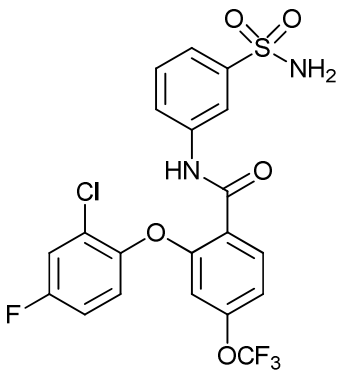


2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide;



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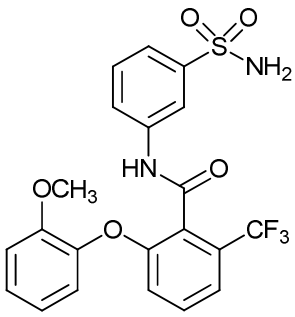

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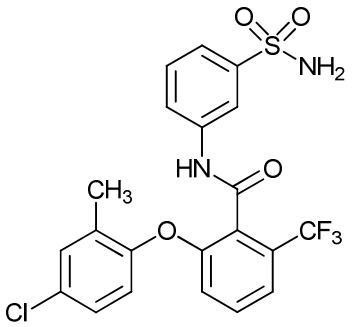
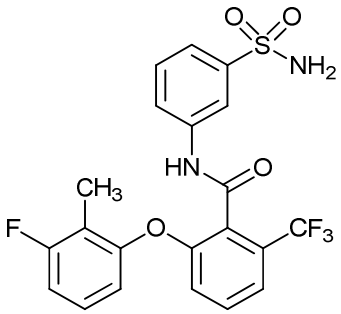


2-(4-chloro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide;



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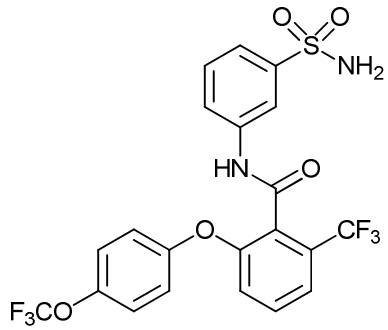
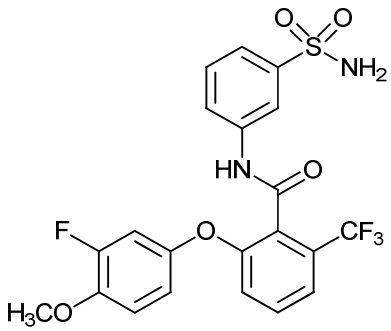
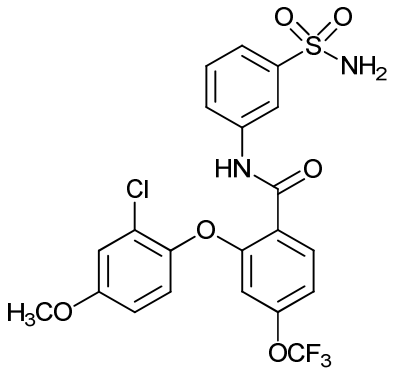


N-(3-sulfamoylphenyl)-2-(4-(trifluoromethoxy)phenoxy)-6-(trifluoromethyl)benzamide;



2-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide;



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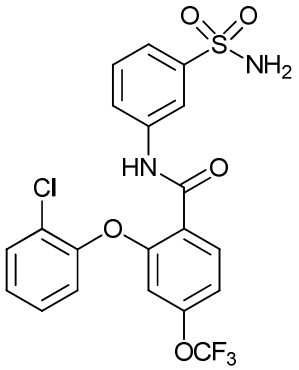
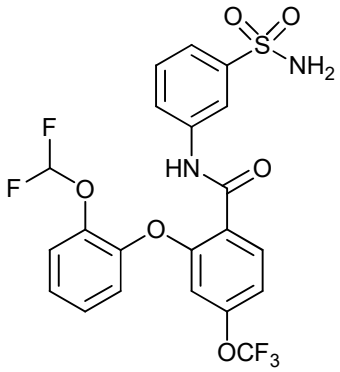


2-(2-chlorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide;



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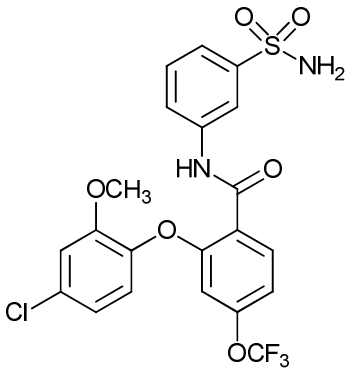

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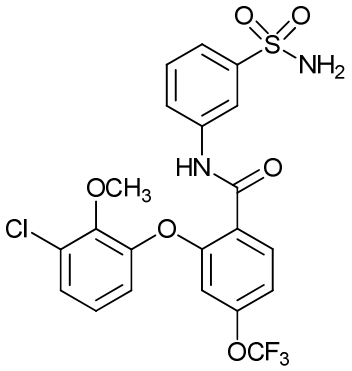

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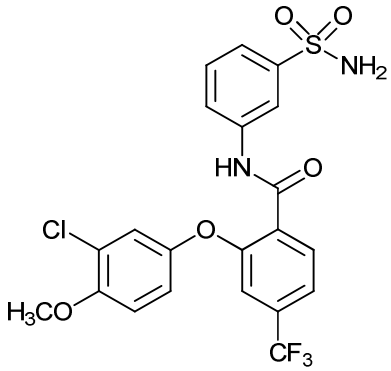

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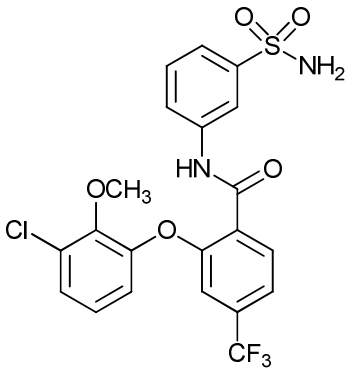

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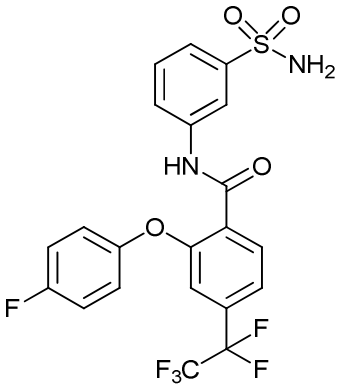

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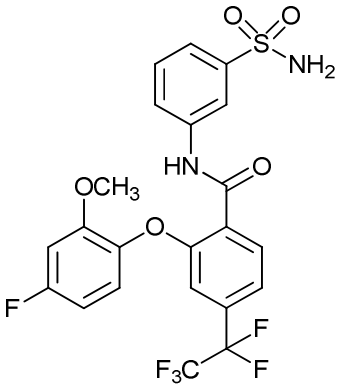

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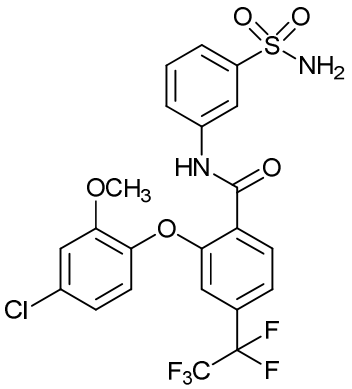

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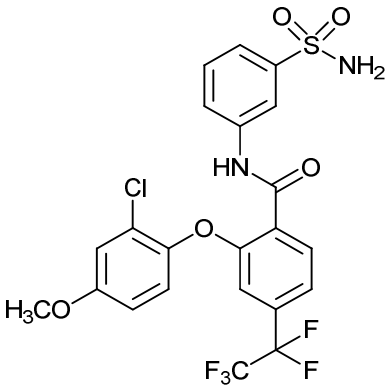

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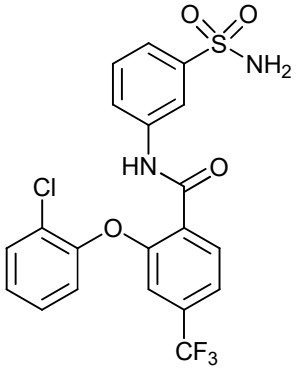

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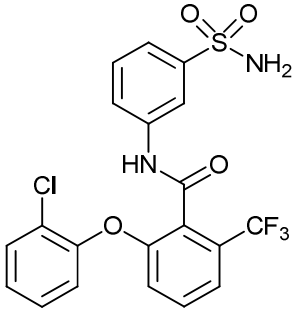

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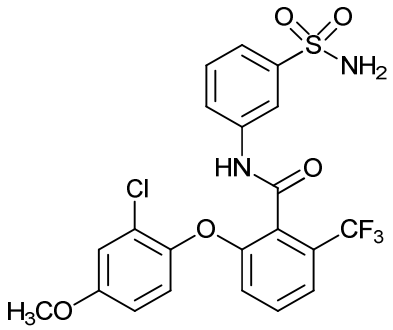

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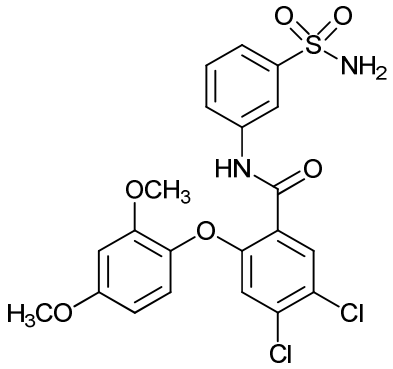

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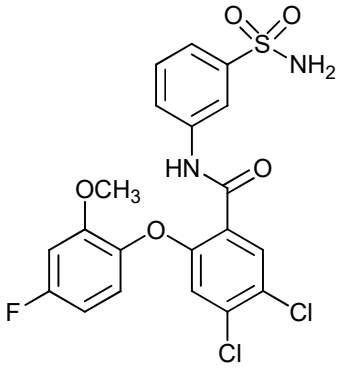

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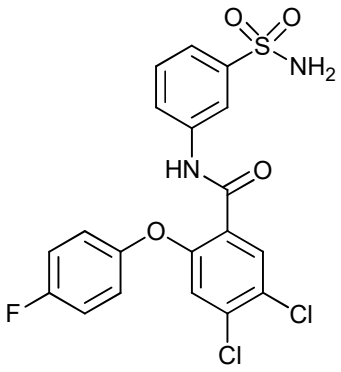

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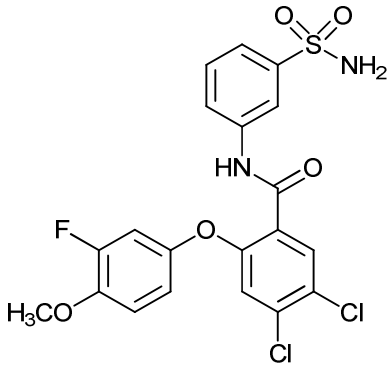

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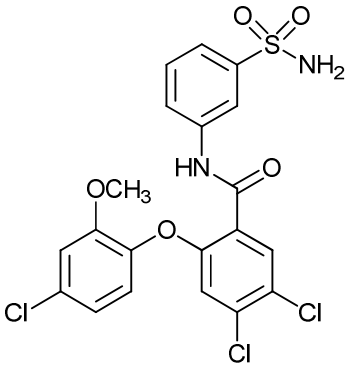

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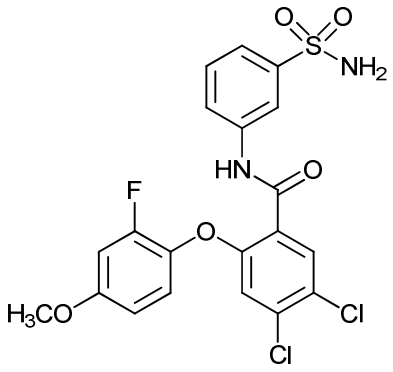

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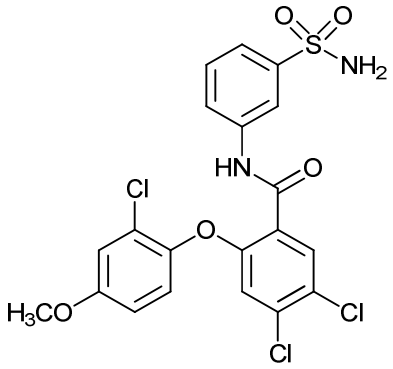

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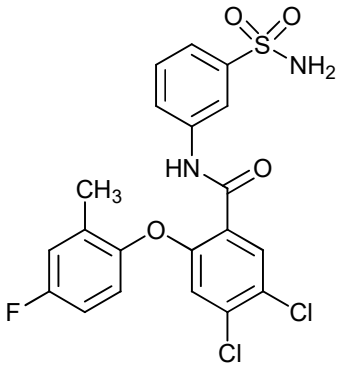

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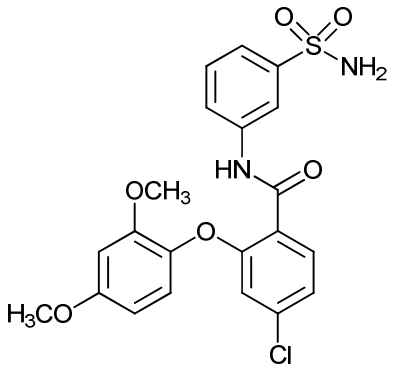

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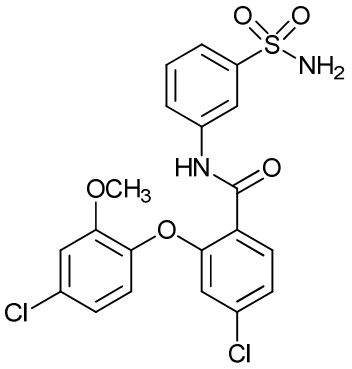

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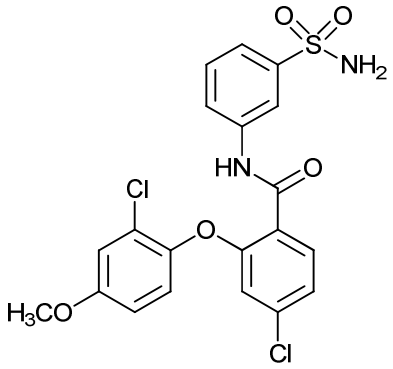

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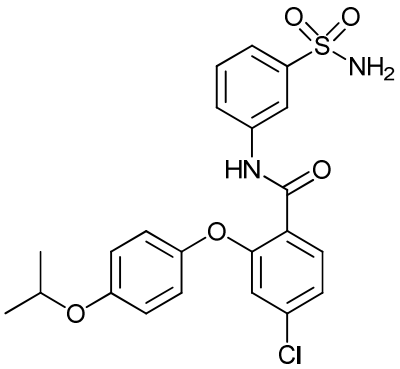

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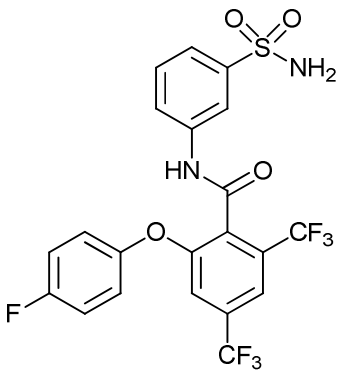
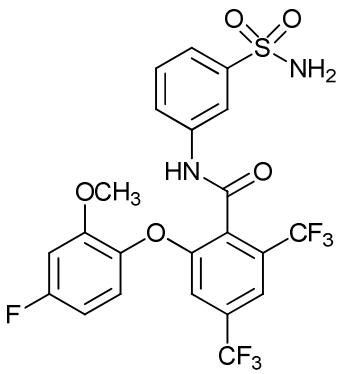


2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide;



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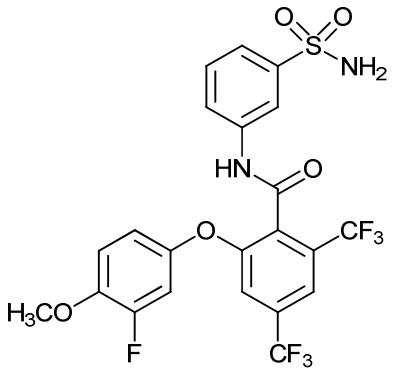

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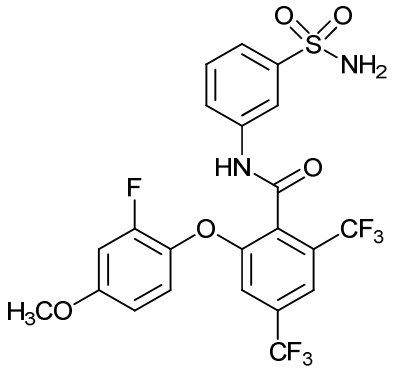

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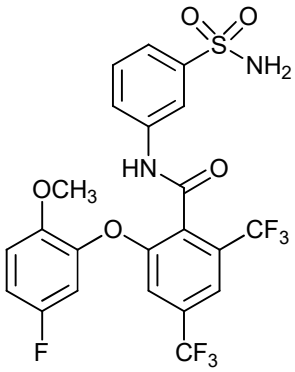

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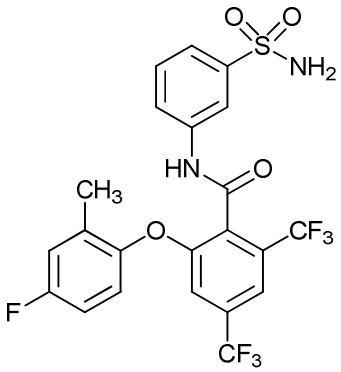

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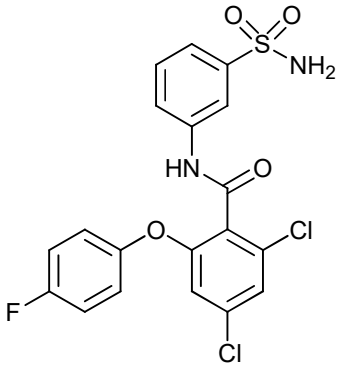

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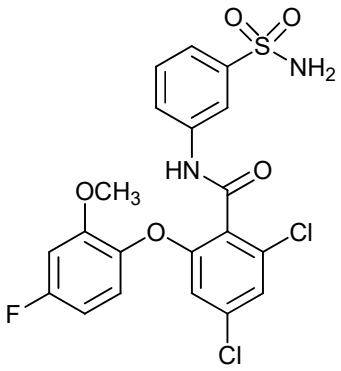

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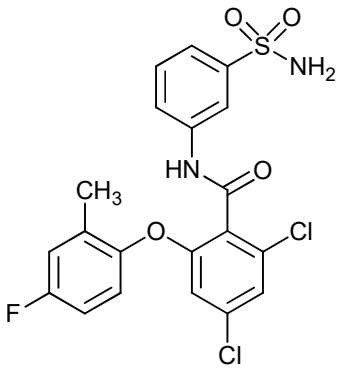

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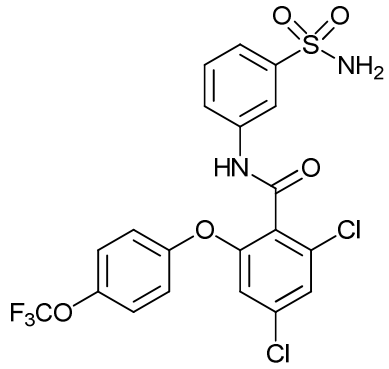
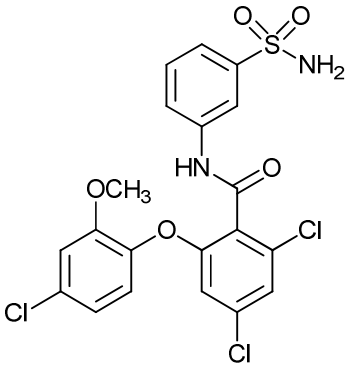


2,4-dichloro-N-(3-sulfamoylphenyl)-6-(4-(trifluoromethoxy)phenoxy)benzamide;



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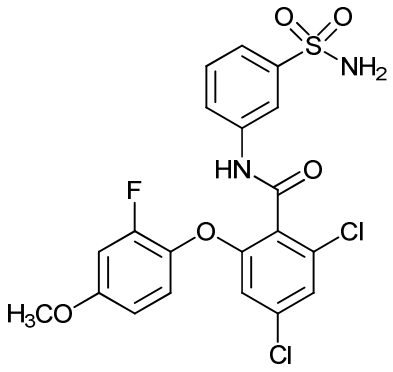
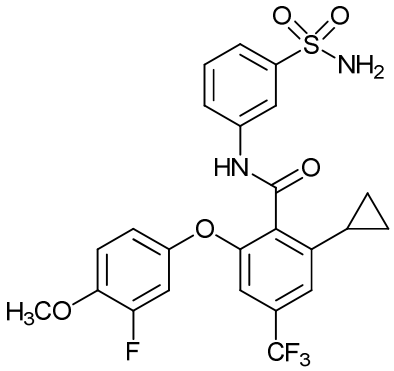


2,4-dichloro-6-(2-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide; and



2-cyclopropyl-6-(3-fluoro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide.

22. A pharmaceutical composition comprising a therapeutically effective amount of the compound or the pharmaceutically acceptable salt thereof of any one of claims 1 to 20 or the compound of claim 21 and one or more pharmaceutically acceptable carriers or vehicles.

23. A pharmaceutical composition comprising the compound or the pharmaceutically acceptable salt thereof of any one of claims 1 to 20 or the compound of claim 21 and one or more pharmaceutically acceptable carriers or vehicles.

24. Use of the compound or the pharmaceutically acceptable salt thereof of any one of claims 1 to 20, the compound of claim 21 or the pharmaceutical composition according to claim 22 or 23 in the manufacture of a medicament for inhibiting a voltage-gated sodium channel in a subject.

25. The use of claim 24, wherein the voltage-gated sodium channel is Nav1.8.

26. Use of the compound or the pharmaceutically acceptable salt thereof of any one of claims 1 to 20, the compound of claim 21 or the pharmaceutical composition according to claim 22 or 23 in the manufacture of a medicament for treating or lessening the severity in a subject of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain, visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence or cardiac arrhythmia.

27. The use of claim 26, wherein the gut pain comprises inflammatory bowel disease pain, Crohn's disease pain or interstitial cystitis pain.

28. The use of claim 26, wherein neuropathic pain comprises post-herpetic neuralgia, diabetic neuralgia, painful HIV-associated sensory neuropathy, trigeminal neuralgia, burning mouth syndrome, post-amputation pain, phantom pain, painful neuroma; traumatic neuroma; Morton's neuroma; nerve entrapment injury, spinal stenosis, carpal tunnel syndrome, radicular pain, sciatica pain; nerve avulsion injury, brachial plexus avulsion injury; complex regional pain syndrome, drug therapy induced neuralgia, cancer chemotherapy induced neuralgia, anti-retroviral therapy induced neuralgia; post spinal cord injury pain, idiopathic small-fiber neuropathy, idiopathic sensory neuropathy or trigeminal autonomic cephalalgia.

29. The use of claim 28, wherein neuropathic pain comprises idiopathic small-fiber neuropathy.

30. The use of claim 28, wherein neuropathic pain comprises post-herpetic neuralgia.

31. The use of claim 26, wherein the musculoskeletal pain comprises osteoarthritis pain, back pain, cold pain, burn pain or dental pain.

32. The method of claim 31, wherein musculoskeletal pain comprises osteoarthritis pain.

33. The use of claim 26, wherein the inflammatory pain comprises rheumatoid arthritis pain or vulvodynia.

34. The use of claim 26, wherein the idiopathic pain comprises fibromyalgia pain.

35. The use of claim 26, wherein the medicament is for treating or lessening the severity in the subject of acute pain.

36. The use of claim 35, wherein the acute pain comprises acute post-operative pain.

37. The use of claim 26, wherein the medicament is for treating or lessening the severity in the subject of postsurgical pain.

38. The use of claim 26, wherein the medicament is for treating or lessening the severity in the subject of visceral pain.

39. The use of claim 26, wherein the medicament is for treating or lessening the severity in the subject of neuropathic pain, wherein the neuropathic pain is diabetic neuropathy.

40. Use of the compound or the pharmaceutically acceptable salt thereof of any one of claims 1 to 20, the compound of claim 21 or the pharmaceutical composition according to claim 22 or 23 in the manufacture of a medicament for treating or lessening the severity in a subject of pain.

41. The use according to any one of claims 24 to 40, wherein the medicament is to be administered to said subject in conjunction with one or more additional therapeutic agents to be administered concurrently with, prior to, or subsequent to treatment with the medicament comprising the compound, pharmaceutically acceptable salt, or pharmaceutical composition.

42. The compound or the pharmaceutically acceptable salt thereof of any one of claims 1 to 20, the compound of claim 21, or the pharmaceutical composition according to claim 22 or 23, for use as a medicament.

42. The compound according to claim 1, substantially as herein described with reference to any one of the examples thereof.